b 8239
507053
he0113

ห้องสมุด ๑๐๐ ปี เสม พริ้งพวงแก้ว

International Guidelines on Research Ethics

Nuremberg Code
Declaration of Helsinki (1964, 1983, 1989, 1996, 2000)
Belmont Report
ICH-GCP Guidelines
WHO GCP Guidelines
Operational Guidelines for Ethics Committees That Review Biomedical Research
Surveying and Evaluating Ethical Review Practices
Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Board
CIOMS Guidelines 2002
Nuffield Council Guidelines on Bioethics

เลขหมู่ W20.55.H9 I181I 2002
เลขทะเบียน he0113
วันที่ 15 ก.ค. 2555

สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์
Institute for Development of Human Rasearch Protection

คำนำ

สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์ เป็นหน่วยงานตั้งใหม่ภายใต้สถาบันวิจัยระบบสาธารณสุข ชื่อย่อเรียกว่า สคม. ชื่อภาษาอังกฤษว่า Institute for Development of Human Research Protection ชื่อย่อภาษาอังกฤษเรียกว่า IHRP มีวัตถุประสงค์ ดังนี้

1) พัฒนากฎหมายเกี่ยวกับการวิจัยในมนุษย์
2) พัฒนาข้อเสนอนโยบายด้านการวิจัยในมนุษย์
3) พัฒนามาตรฐาน หลักเกณฑ์ และแนวทางการวิจัยในมนุษย์
4) กระตุ้นให้เกิดการพัฒนาการคุ้มครองการวิจัยในมนุษย์
5) เป็นศูนย์รวมองค์ความรู้ด้านการคุ้มครองการวิจัยในมนุษย์
6) ทบทวน พิจารณา ให้การรับรอง และเสนอแนะโครงการวิจัยในมนุษย์ ในลักษณะพหุสถาบัน หรือการวิจัยในมนุษย์ที่ต้องการการทบทวนพิจารณา และรับรองในระดับชาติ
7) กระทำการอื่นตามที่คณะกรรมการสถาบันวิจัยระบบสาธารณสุขกำหนด หรือมอบหมาย

งานชิ้นแรกของสถาบันแห่งนี้ คือ การรวบรวมและเผยแพร่หลักเกณฑ์สากล หรือที่ยอมรับในระดับสากล ที่ได้รับการอ้างอิงอย่างกว้างขวางทั่วโลก ได้แก่

1) Nuremberg Code 1947
2) Declaration of Helsinki
3) Belmont Report
4) ICH – GCP Guidelines
5) WHO – GCP Guidelines
6) Operational Guidelines for Ethics Committees That Review Biomedical Research
7) Surveying and Evaluating Ethical Review Practices
8) Operational Guidelines for The Establishment and Functioning of Data and Safety Monitoring Boards
9) CIOMS Guidelines 2002
10) Nuffield Council on Bioethics

ทั้งนี้เพื่อให้ผู้มีหน้าที่เกี่ยวข้องสามารถศึกษาและใช้อ้างอิงได้โดยสะดวก โดยเฉพาะ Declaration of Helsinki ได้จัดพิมพ์ไว้ทุกฉบับ ตั้งแต่ฉบับแรกที่ประกาศเมื่อปี ค.ศ. 1964 และได้เปรียบเทียบฉบับปี ค.ศ. 1996 กับ ฉบับปี ค.ศ. 2000 ซึ่งเป็นฉบับล่าสุดไว้ด้วย เพื่อให้เห็นวิวัฒนาการของหลักเกณฑ์จริยธรรมสากลที่ได้รับการยอมรับอย่างกว้างขวางที่สุด และยาวนานที่สุดฉบับนี้

เชื่อว่าผู้เกี่ยวข้องกับการวิจัยในมนุษย์ตั้งแต่ นักวิจัย กรรมการจริยธรรมการวิจัย สถาบันที่วิจัย หน่วยควบคุมทางกฎหมาย ผู้บริหาร นักวิชาการ นักศึกษา และประชาชนทั่วไป จะได้ประโยชน์จากเอกสารฉบับนี้พอสมควร สถาบันมีโครงการจะแปลเอกสารเหล่านี้ออกเป็นภาษาไทยต่อไป เพื่อให้ง่ายสำหรับผู้ที่จำเป็นต้องศึกษาแต่อาจไม่คุ้นเคยกับภาษาอังกฤษอย่างเช่น อาสาสมัครวิจัย และกรรมการวิจัยในคนที่มิใช่นักวิชาการหรือผู้เชี่ยวชาญ เป็นต้น

สิงหาคม 2550

CONTENTS

International Guidelines in Biomedical Research

1. Nuremberg Code 1
2. Declaration of Helsinki (1964, 1983, 1989, 1996, 2000) 5
3. Belmont Report 29
4. ICH-GCP Guidelines 45
5. WHO Guidelines 97
   a. WHO GCP Guidelines 99
   b. Operational Guidelines for Ethics Committees That Review Biomedical Research 135
   c. Surveying and Evaluating Ethical Review Practices 173
   d. Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards 203
6. CIOMS Guidelines 2002 247
7. Nuffield Council on Bioethics 311

Nuremberg Code

CIRP Introduction

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects in a new code that is now accepted worldwide.

This judgment established a new standard of ethical medical behavior for the post World War II human rights era. Amongst other requirements, this document enunciates the requirement of *voluntary informed consent* of the human subject. The principle of voluntary informed consent protects the right of the individual to control his own body.

This code also recognizes that the risk must be weighed against the expected benefit, and that unnecessary pain and suffering must be avoided.

This code recognizes that doctors should avoid actions that injure human patients.

The principles established by this code for medical practice now have been extened into general codes of medical ethics.

The Nuremberg Code (1947)

Permissible Medical Experiments

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

For more information see Nuremberg Doctor's Trial, *BMJ* 1996;313(7070):1445-75.

Declaration of Helsinki 2000

Declaration of Helsinki 2000

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then

obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing

health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Page back to paragraph 29.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Page back to paragraph 30.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004

Declaration of Helsinki (1964)

[CIRP Note: Ethical research on human subjects into or about the effects of circumcision must be conducted under the provisions of this declaration and those of the *Nuremberg Code*.]

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland,June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration,"and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient. "

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all

over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the law of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject mustbe adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw visor her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably inheriting.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained

by a physician who isn't engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient- including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge,only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers- either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Cite as:

- World Medical Organization. Declaration of Helsinki. *British Medical Journal* (7 December) 1996;313(7070):1448-1449.

DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembley, Helsinki, Finland, June 1964,
amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975,
and the 35th World Medical Assembly, Venice, Italy, October 1983

Contents

- INTRODUCTION
- I. BASIC PRINCIPLES
- II. MEDICIAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)
- III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

INTRODUCTION

It ist the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely indepentent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICIAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

The World Medical Association Declaration of Helsinki

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical

Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free

to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

January 8, 2001. Glen Drew This is a draft prepared for the National Bioethics Advisory Commission and therefore does not represent final conclusions. It should not be cited or referenced as such.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
Ethical Principles for Medical Research Involving Human Subjects	Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects
A. INTRODUCTION	**Introduction**
1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.	Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.	It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."	The Declaration of Geneva of the World Medical Association binds the physician with the words, ``The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, ``A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.	Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.	III.4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.	The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.	In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care	
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.	
	In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.
B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH	**I. Basic Principles**
10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject	III.1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.	I.1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.	Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.	I.2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration	I.12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.	I.3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.	I.5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.	I.7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.	I.4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.	
20. The subjects must be volunteers and informed participants in the research project.	III.2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.	I.6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.	I.9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.	I.10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons. 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.	I.11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.	II.5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.	I.8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE	**II. Medical Research Combined with Professional Care (Clinical Research)**
28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.	II.6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

2000 Order - Side-by-Side Comparison of 1996 and 2000 Declaration of Helsinki

2000 Version	1996 Version
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.	II.2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
	II.3. In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.	
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.	II.4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.	II.1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
	III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)
	III.3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

The Belmont Report

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the

Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
****Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*
**** Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

**** Deceased.*

Table of Contents

Ethical Principles and Guidelines for Research Involving Human Subjects
A. Boundaries Between Practice and Research
B. Basic Ethical Principles

1. Respect for Persons
2. Beneficence
3. Justice
C. Applications
1. Informed Consent
2. Assessment of Risk and Benefits
3. Selection of Subjects

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

[RETURN TO TABLE OF CONTENTS]

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions

in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to

explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized

and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making

decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

---

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit

some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

International Conference on Harmonization Guidance E6: Good Clinical Practice Consolidated Guidelines

International Conference on Harmonization Guidance E6: Good Clinical Practice: Consolidated Guidelines

TABLE OF CONTENTS

INTRODUCTION

1. GLOSSARY

2. THE PRINCIPLES OF ICH GCP

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.2 Composition, Functions and Operations

3.3 Procedures

3.4 Records

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communication with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed Consent of Trial Subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.2 Contract Research Organization (CRO)

5.3 Medical Expertise

5.4 Trial Design

5.5 Trial Management, Data Handling, and Record Keeping

5.6 Investigator Selection

5.7 Allocation of Responsibilities

5.8 Compensation to Subjects and Investigators

5.9 Financing

5.10 Notification/Submission to Regulatory Authority(ies)

5.11 Confirmation of Review by IRB/IEC

5.12 Information on Investigational Product(s)

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.14 Supplying and Handling Investigational Product(s)

5.15 Record Access

5.16 Safety Information

5.17 Adverse Drug Reaction Reporting

5.18 Monitoring

5.18.1 Purpose

5.18.2 Selection and Qualifications of Monitors

5.18.3 Extent and Nature of Monitoring

5.18.4 Monitor's Responsibilities

5.18.5 Monitoring Procedures

5.18.6 Monitoring Report

5.19 Audit

5.19.1 Purpose

5.19.2 Selection and Qualification of Auditors

5.19.3 Auditing Procedures

5.20 Noncompliance

5.21 Premature Termination or Suspension of a Trial

5.22 Clinical Trial/Study Reports

5.23 Multicentre Trials

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

6.1 General Information

6.2 Background Information

6.3 Trial Objectives and Purpose

6.4 Trial Design

6.5 Selection and Withdrawal of Subjects

6.6 Treatment of Subjects

6.7 Assessment of Efficacy

6.8 Assessment of Safety

6.9 Statistics

6.10 Direct Access to Source Data/Documents

6.11 Quality Control and Quality Assurance Procedures

6.12 Ethics

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

6.15 Publication Policy

6.16 Supplements

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

7.2 General Considerations

7.2.1 Title Page

7.2.2 Confidentiality Statement

7.3 Contents of the Investigator's Brochure

7.3.1 Table of Contents

7.3.2 Summary

7.3.3 Introduction

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

7.3.5 Nonclinical Studies

7.3.6 Effects in Humans

7.3.7 Summary of Data and Guidance for the Investigator

7.4 Appendix 1: Title Page (Example)

7.5 Appendix 2: Table of Contents of Investigator's Brochure (Example)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

8.2 Before the Clinical Phase of the Trial Commences

8.3 During the Clinical Conduct of the Trial

8.4 After Completion or Termination of the Trial

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP guidance document is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance document was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guidance document should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guidance document may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for *Structure and Content of Clinical Study Reports*).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance document.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure)

1.37 Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in

other protocol referenced documents. Throughout the ICH GCP Guidance the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guidance the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

results in death,

is life-threatening,

requires inpatient hospitalization or prolongation of existing hospitalization,

results in persistent or significant disability/incapacity,

or

is a congenital anomaly/birth defect

(see the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site

The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

1.61 Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

approval/favourable opinion;

modifications required prior to its approval/favourable opinion;

disapproval/negative opinion; and

termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a nonscientific area.

c. At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate

immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

a. Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

b. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

c. All adverse drug reactions (ADRs) that are both serious and unexpected.

d. New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

a. Its trial-related decisions/opinions.

b. The reasons for its decisions/opinions.

c. Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a. to the IRB/IEC for review and approval/favourable opinion,

b. to the sponsor for agreement and, if required,

c. to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

h. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j. The compensation and/or treatment available to the subject in the event of trial-related injury.

k. The anticipated prorated payment, if any, to the subject for participating in the trial.

l. The anticipated expenses, if any, to the subject for participating in the trial.

m. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

o. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

p. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

s. The expected duration of the subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a. The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

b. The foreseeable risks to the subjects are low.

c. The negative impact on the subject's well-being is minimized and low.

d. The trial is not prohibited by law.

e. The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guidance document also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guidance for *Structure and Content of Clinical Study Reports*, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

b. Maintains SOPs for using these systems.

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

d. Maintain a security system that prevents unauthorized access to the data.

e. Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

f. Maintain adequate backup of the data.

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory
requirement(s).

5.5.11 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

a. to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

b. to comply with procedures for data recording/reporting;

c. to permit monitoring, auditing and inspection (see 4.1.4) and

d. to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related responsibilities.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s))to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

a. The name and address of the investigator's/institution's IRB/IEC.

b. A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

c. Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in

accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

a. Ensure timely delivery of investigational product(s) to the investigator(s).

b. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

c. Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

d. Maintain a system for the position of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

a. Take steps to ensure that the investigational product(s) are stable over the period of use.

b. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.*

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

a. The rights and well-being of human subjects are protected.

b. The reported trial data are accurate, complete, and verifiable from source documents.

c. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

a. Monitors should be appointed by the sponsor.

b. Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

c. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a. Acting as the main line of communication between the sponsor and the investigator.

b. Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

c. Verifying, for the investigational product(s):

   i. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

   ii. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

   iii. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

   iv. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

   v. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

e. Verifying that written informed consent was obtained before each subject's participation in the trial.

f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

g. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

i. Verifying that the investigator is enrolling only eligible subjects.

j. Reporting the subject recruitment rate.

k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

    i. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

    ii. Any dose and/or therapy modifications are well documented for each of the trial subjects.

    iii. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

    iv. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

    v. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

p. Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

a. The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

b. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

c. Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

d. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

a. The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

b. The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

a. The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

b. The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

c. The observations and findings of the auditor(s) should be documented.

d. To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

e. When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial.

When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guidance for *Structure and Content of Clinical Study Reports*. (NOTE: The ICH Guidance for *Structure and Content of Clinical Study Reports* specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial
site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

a. Randomization.

b. Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

a. When and how to withdraw subjects from the trial/ investigational product treatment.

b. The type and timing of the data to be collected for withdrawn subjects.

c. Whether and how subjects are to be replaced.

d. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance Procedures

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for *Structure and Content of Clinical Study Reports*.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guidance delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guidance.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product'(s') pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

Species tested

Number and sex of animals in each group

Unit dose (e.g., milligram/kilogram (mg/kg))

Dose interval

Route of administration

Duration of dosing

Information on systemic distribution

Duration of post-exposure follow-up

Results, including the following aspects:

Nature and frequency of pharmacological or toxic effects
Severity or intensity of pharmacological or toxic effects
Time to onset of effects
Reversibility of effects
Duration of effects
Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a. *Nonclinical Pharmacology*

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b. *Pharmacokinetics and Product Metabolism in Animals*

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c. *Toxicology*

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g., irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.

a. *Pharmacokinetics and Product Metabolism in Humans*

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b. *Safety and Efficacy*

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c. *Marketing Experience*

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 Appendix 1: Title Page (*Example*)

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 Appendix 2: Table of Contents of Investigator's Brochure (*Example*)

Confidentiality Statement (optional)

Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies

   5.1 Nonclinical Pharmacology

   5.2 Pharmacokinetics and Product Metabolism in Animals

   5.3 Toxicology

6. Effects in Humans

   6.1 Pharmacokinetics and Product Metabolism in Humans

   6.2 Safety and Efficacy

   6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on

1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.2.1 INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/ amendment(s) and CRF	X	X
8.2.3 INFORMATION GIVEN TO TRIAL SUBJECT			
- **INFORMED CONSENT FORM** (including all applicable translations)	To document the informed consent	X	X
- **ANY OTHER WRITTEN INFORMATION**	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
-ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4 FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator /institution and the sponsor for the trial	X	X
8.2.5 INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6 SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:	To document agreements		
- investigator /institution and sponsor		X	X

- investigator/ institution and CRO		X	X (where required)
- sponsor and CRO			X
- investigator/ institution and authority(ies) (where required)		X	X
8.2.7 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	To document that the trial has been subject to IRB/IEC review and given approval/ favourable opinion. To identify the version number and date of the document(s).	X	X
- protocol and any amendments			
- CRF (if applicable)			
- informed consent form(s)			
- any other written information to be provided to the subject(s)			
- advertisement for subject recruitment (if used)			
- subject compensation (if any)			
- any other documents given approval/ favourable opinion			
8.2.8 INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9 REGULATORY AUTHORITY(IES) AUTHORISATION/ APPROVAL/ NOTIFICATION OF PROTOCOL	To document appropriate authorisation/ approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of	X (where required)	X
	the trial in compliance with the applicable regulatory requirement(s)	(where required)	

8.2.10CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11 NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12 MEDICAL /LABORATORY/ TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13 SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED	To document shipment dates, batch numbers and method of shipment of investigational	X	X

MATERIALS	product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability		
8.2.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17 DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19 PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20 TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.3.1 INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it	X	X

	becomes available		
8.3.2 ANY REVISION TO:	To document revisions of these trial related documents that take effect during trial	X	X
- protocol/amendment(s) and CRF			
- informed consent form			
- any other written information provided to subjects			
- advertisement for subject recruitment (if used)			
8.3.3 DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB)/ INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the ocument(s).	X	X
- protocol amendment(s)			
- revision(s) of:			
- informed consent form			
- any other written information to be provided to the subject			
- advertisement for subject recruitment (if used)			
- any other documents given approval /favourable opinion			
- continuing review of trial (where required)			
8.3.4 REGULATORY AUTHORITY(IES) AUTHORISATIONS/ APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR:	To document compliance with applicable regulatory requirements	X (where required)	X
- protocol amendment(s) and			

other documents			
8.3.5 CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB- INVESTIGATOR(S)	(see 8.2.10)	X	X
8.3.6 UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S)/ TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7 UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8 DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15)	X	X
8.3.9 CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16)		X
8.3.10 MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11 RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X

- meeting notes - notes of telephone calls			
8.3.12 SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13 SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14 SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15 DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16 NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17 NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and	X (where required)	X

REACTIONS AND OF OTHER SAFETY INFORMATION	4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2		
8.3.18 NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19 INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20 SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21 SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
8.3.22 SUBJECT ENROLLMENT LOG	To document chronological enrollment of subjects by trial number	X	
8.3.23 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24 SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25 RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.4.1 INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2 DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3 COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4 AUDIT CERTIFICATE (if available)	To document that audit was performed		X
8.4.5 FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6 TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X
8.4.7 FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND	To document completion of the trial	X	

WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)			
8.4.8 CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X

WHO GCP Guidelines

World Health Organization
WHO Technical Report Series, No. 850, 1995, Annex 3

Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*

INTRODUCTION

Glossary

1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL
   - 1.1 Justification for the trial
   - 1.2 Ethical principles
   - 1.3 Supporting data for the investigational product
   - 1.4 Investigator and site(s) of investigation
   - 1.5 Regulatory requirements

2. THE PROTOCOL

3. PROTECTION OF TRIAL SUBJECTS
   - 3.1 Declaration of Helsinki
   - 3.2 Ethics committee
   - 3.3 Informed consent
   - 3.4 Confidentiality

4. RESPONSIBILITIES OF THE INVESTIGATOR
   - 4.1 Medical care of trial subjects
   - 4.2 Qualifications
   - 4.3 Selection of trial subjects
   - 4.4 Compliance with the protocol
   - 4.5 Information for subjects and informed consent
   - 4.6 The investigational product
   - 4.7 The trial site
   - 4.8 Notification of the trial or submission to the drug regulatory authority
   - 4.9 Review by an ethics committee
   - 4.10 Serious adverse events or reactions
   - 4.11 Financing
   - 4.12 Monitoring, auditing and inspection
   - 4.13 Record-keeping and handling of data
   - 4.14 Handling of and accountability for pharmaceutical products for trial
   - 4.15 Termination of trial
   - 4.16 Final report
   - 4.17 Trials in which the investigator is the sponsor

5. RESPONSIBILITIES OF THE SPONSOR
   - 5.1 Selection of the Investigator(s)
   - 5.2 Delegation of responsibilities
   - 5.3 Compliance with the protocol and procedures
   - 5.4 Product information
   - 5.5 Safety information
   - 5.6 Investigational product
   - 5.7 Trial management and handling of data
   - 5.8 Standard operating procedures
   - 5.9 Compensation for subjects and investigators
   - 5.10 Monitoring
   - 5.11 Quality assurance
   - 5.12 Study reports
   - 5.13 Handling of adverse events

5.14 Termination of trial

6. RESPONSIBILITIES OF THE MONITOR
6.1 Qualifications
6.2 Assessment of the trial site
6.3 Staff education and compliance
6.4 Data management
6.5 Case-report forms
6.6 Investigational product
6.7 Communication
6.8 Notification of the trial or submission to the regulatory authority
6.9 Reports

7. MONITORING OF SAFETY
7.1 Handling and recording adverse events
7.2 Reporting adverse events

8. RECORD-KEEPING AND HANDLING OF DATA
8.1 Responsibilities of the investigator
8.2 Responsibilities of the sponsor and the monitor
8.3 Archiving of data

9. STATISTICS AND CALCULATIONS
9.1 Experimental design
9.2 Randomization and blinding
9.3 Statistical analysis

10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS
10.1 Supply and storage
10.2 Investigational labelling and packaging
10.3 Responsibilities of the investigator
10.4 Responsibilities of the sponsor and the monitor

11. ROLE OF THE DRUG REGULATORY AUTHORITY
11.1 General responsibilities
11.2 On-site inspections

12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

13. CONSIDERATIONS FOR MULTICENTRE TRIALS

REFERENCES

APPENDIX 1. World Medical Association's Declaration of Helsinki

APPENDIX 2. Model list of items to be contained in a clinical trial protocol

APPENDIX 3. Considerations for multicentre trials

** This text was developed in consultation with national drug regulatory authorities within WHO's Member States. It was also discussed during two informal consultations convened by the Division of Drug Management and Policies, WHO, Geneva, from 26 to 27 June 1991 and 29 June*

to 3 July 1992. The participants were: Ms M. Cone, International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva, Switzerland; Professor P. Dayer, International Union of Pharmacology (IUPHAR), Brussels, Belgium; Professor I. Darmansjah, University of Jakarta, akarta, Indonesia; Dr J.F. Dunne, Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland (Joint Secretary); Dr Y. Hirayama, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Professor E. Hvidberg, University Hospital, Copenhagen, Denmark (Chairman); Dr J. Idänpään-Heikkilä, Associate Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland (Joint Secretary); Mr R. Laderman, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA; Professor V.H. Lepakhin, Russian State Center for Drug Expertise, Moscow, Russian Federation; Dr P. Maurice, Ciba-Geigy, Basel, Switzerland; Professor J.O.M. Pobee, School of Medicine, Lusaka, Zambia; Mr M. Tsukano, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Dr S. Westman-Naeser, Medical Products Agency, Uppsala, Sweden; Professor A. Zanini, Institute of Biomedical Science, São Paulo, Brazil; Professor Zhu Jun-Ren, Shanghai Medical University, Shanghai, China.

INTRODUCTION

The purpose of these WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products is to set globally applicable standards for the conduct of such biomedical research on human subjects. They are based on provisions already promulgated in a number of highly developed countries including Australia, Canada, European Community countries, Japan, Nordic Countries (Denmark, Finland, Iceland, Norway and Sweden) and the United States. These guidelines inevitably vary somewhat in content and emphasis, but all are consonant with regards to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the interested countries. Every care has been taken, in developing the WHO Guidelines as a practicable administrative tool for use by WHO's Member States, to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultation, to seek formal acceptance of the Guidelines by Member States as a contribution to harmonization of national standards and to facilitating movement of pharmaceutical prod cts internationally. No question arises, however, of challenging or replacing existing national egulations or requirements. The objective is to provide a complementary standard that can be applied worldwide. In countries where national regulations or requirements do not exist or require supplementation, relevant government officials may designate or adopt, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted.

The Guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, but protect the rights and safety of subjects, including patients, and ensure that the investigations are directed to the advancement of public health objectives.

The Guidelines are intended specifically to be applied during all stages of drug development both prior to and subsequent to product registration and marketing, but they are also applicable, in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and, in particular, to every newly-trained doctor.

Glossary

The definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

adverse event
Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

adverse reaction
A response to a pharmaceutical product that is noxious and unintended and which occurs at doses normally used or tested in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse or dependence and interactions with any other product should be considered adverse reactions.

audit of a trial
A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms (CRFs) are consonant with those found in hospital files and other original records.

case -report form (CRF)
A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

clinical trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:

Phase I
These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

Phase II
These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III
Trials in larger (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV
Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should

use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

comparator product
A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

confidentiality
Maintenance of the privacy of trial subjects including their personal identity and all personal medical information.

contract
A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.

contract research organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

escape treatment
Any supplementary treatment provided to relieve the trial subject of symptoms caused by the investigated disease in the clinical trial. Escape treatment is often used in order to alleviate pain in placebo-controlled trials.

ethics committee
An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report
A comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal.

Good Clinical Practice (GCP)
A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP Guidelines published by WHO *(1)*.

informed consent

A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (see Appendix 1).

inspection
An officially-conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in this document.

investigator
A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

investigational labelling
Labelling developed specifically for products involved in a clinical trial.

investigational product (synonym: study product)
Any pharmaceutical product (see definition) or placebo being tested or used as a reference in a clinical trial.

investigator's brochure
A collection of data for the investigator consisting of all the relevant information on the investigational product(s), including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated.

monitor
A person appointed by, and responsible to, the sponsor or Contract Research Organization (CRO) for the monitoring and reporting of progress of the trial and for verification of data.

patient/subject file
A collection of data consisting of all relevant information on the patient or subject (such as hospital file, consultation records or special subject file) that permits the authenticity of the information presented in case-record forms to be verified and, where necessary, completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

pharmaceutical product
Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

protocol

A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

quality assurance relating to clinical trials
Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting, and professional or personnel qualifications.

raw data
All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies in the form of photocopies, microfiches etc. Raw data can also include photographic negatives, microfilm or magnetic media (e.g. computer diskettes).

serious adverse event
An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures (SOP)
Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

study product (synonym: investigational product)
Any pharmaceutical product or placebo being tested or used as reference in a clinical trial.

trial subject
An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control The individual may be:
- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational product;
- a person (usually a patient) whose condition is relevant to the use of the investigational product.

validation
Action of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

verification (validation) of data
The procedures carried out to ensure that the data contained in the final report match original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer print-outs and statistical analyses and tables.

witness
A person who will not be influenced in any way by those who are involved in the clinical trial, who is present and may provide assistance if required when the subject's informed consent is obtained, and documents that this consent is given freely by signing and dating the informed-consent form.

1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

1.1 *Justification for the trial*
It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified.

1.2 *Ethical principles*
All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki (see Appendix 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) and non-maleficence (doing no harm) as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS)*(2)* or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles. (See chapters 3 and 4).

1.3 *Supporting data for the investigational product*
Pre-clinical studies that provide sufficient documentation of potential safety and eventual clinical application of a pharmaceutical product are a prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that the it is of suitable quality for the intended investigational use. The pharmaceutical, pre-clinical and clinical data should be adapted to the appropriate phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for the planning and conducting of subsequent trials.

1.4 *Investigator and site(s) of investigation*
Each investigator should have appropriate expertise, qualifications and competence to undertake a proposed study.Prior to the trial, the investigator(s) and the sponsor should establish an agreement on the protocol, standard operating procedures (SOP), the monitoring, and auditing of the trial, and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently (see chapter 4).

1.5 *Regulatory requirements*
Countries in which clinical trials are performed should have regulations governing the way in which these studies can be conducted. The pre-trial agreement between the sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application to or notification of the trial to the relevant authority, amendments to the trial protocol, reporting of all adverse events, and notifications to ethics committee). All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In countries where regulations do not exist or require supplementation, relevant government officials may designate, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted. The use of these Guidelines should not prevent their eventual adaptation into national regulations or laws. Neither should they be used to supersede an existing national requirement in countries where the national requirement is more rigorous.

2. THE PROTOCOL

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used; the reasons for proposing that it should be undertaken on humans; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. Other important items to be included in a clinical trial protocol are listed in Appendix 2.

The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations), review bodies (e.g. institutional review board, peer review committee, ethics committee, drug regulatory authority), constituted appropriately for this purpose and independent of the investigator(s) and sponsor.

3. PROTECTION OF TRIAL SUBJECTS

The personal integrity and welfare of the trial subjects as defined in the Declaration of Helsinki should be the primary concern of all parties involved in the conduct of a clinical trial and the review of the protocol but it is the ultimate responsibility of the investigator, who must also take into consideration the scientific validity of the trial.

3.1 *Declaration of Helsinki*

The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials. Any departures from the Declaration must be justified and stated in the protocol. Independent assurance that subjects are protected can only be provided by an ethics committee and freely obtained informed consent.

3.2 *Ethics committee*

The role of the ethics committee (or other board responsible for reviewing the trial) is to ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, inter alia, by previewing trial protocols, etc. (see Section 2).

The ethics committee should be constituted and operated so that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

The ethics committee should have documented policies and procedures as a basis for its work, which should be available to the public. These should set out the authority under which the committee is established, the number of members elected and their qualifications, a definition of what it will review and its authority to intervene and maintain records of its activities. The documents should also state how frequently the committee will meet and how it interacts with the investigator and/or sponsor.

The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol (including appendices

and amendments) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

The ethics committee has an ongoing responsibility for the ethical conduct of research, and therefore must be informed of all subsequent amendments to the protocol and of any serious adverse events occurring during the trial, or other new information likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be asked for its opinion if a re-evaluation of the ethical aspects of the trial appears to be required, or if there is any doubt regarding the importance of a protocol change or new information.

Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures. The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, itemizing the documents studied and stating the date of review. A list of those present at the committee meeting, including their professional status, should be attached.

When reviewing a clinical trial proposal the ethics committee should consider the following:

a) The acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his or her qualifications, experience, availability for the duration of the study, supporting staff and available facilities.
b) The suitability of the protocol including the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, and the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.
c) The means by which trial subjects will be recruited, necessary or appropriate information will be given, and consent will be obtained. This is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group (see Section 3.3 e–f).
d) The adequacy and completeness of the information, which should be written in a language and at a level of complexity understandable to everyone involved, to be given to the subjects, their relatives, guardians or, if necessary, legal representatives. All such written information must be submitted in its final form to the ethics committee.
e) Provision, if any, for compensation or treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity (a source of legal and financial support) to cover the liability of the investigator(s) and sponsor. (See Section 5.9).
f) The appropriateness of the extent and form of payment through which the sponsor will remunerate or compensate the organization(s) and/or investigator(s) conducting the trial, and the trial subjects, as required by local laws and regulations.
g) The acceptability of proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

3.3 *Informed consent*

The principles of informed consent in the current revisions of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2)* should be implemented in each clinical trial.

a) Information should be given in a language and at a level of complexity understandable to the subject in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, that participation is voluntary and that refusal to participate or withdraw from the trial at any stage will not

prejudice the subject's care, rights and welfare. Subjects must be allowed sufficient time, determined by their health condition and/or the illness, to enquire about details of the trial and to decide whether or not they wish to participate.

b) The subject must be made aware and consent that personal information may be scrutinized during monitoring, auditing or inspection of the trial by properly authorized persons, the sponsor or relevant authorities, and that participation and personal information in the trial will be treated as confidential and will not be publicly available. This principle may be modified by national laws and regulations.

c) The subject must have access to information about insurance, if any, and other procedures for compensation and treatment should he or she be injured or disabled by participating in the trial.

d) If a subject consents to participate after a full and comprehensive explanation of the study, this consent should be appropriately recorded. The explanation should include the aim of the study; the expected benefits for the subjects and/or others; the possibility of allocation to a reference treatment or placebo; the risks and inconveniences – e.g. invasive procedures; and, where appropriate, an explanation of alternative, recognized medical therapy. Consent must be documented either by the subject's dated signature or in agreement with local laws and regulations by the signature of an independent witness who records the subject's consent. In either case, the subject must be informed that signature confirms that the consent is based on information which has been given, and that the subject has freely chosen to participate without prejudice to legal and ethical rights, while reserving the right to withdraw from the study at his or her own initiative at any time, without having to give any reason. If, however, the reason for withdrawal relates to an adverse event(s), the investigator should be informed.

e) Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure – such as medical, pharmacy and nursing students, hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of the hierarchy in case of refusal to participate. Other vulnerable groups whose consent also needs special consideration include patients with incurable diseases, people in nursing homes, prisoners or detainees, the unemployed or people on a very low income, patients in emergency departments, some ethnic and racial minority groups, the homeless, nomads and refugees. If such categories are part of the population to be enrolled in a clinical trial, the ethics committee should consider carefully the appropriateness of the informed-consent process.

f) If the subject is incapable of giving personal consent (e.g. in the case of children or adults who are unconscious or suffering from severe mental illness or disability), the inclusion of such patients in a trial may be acceptable provided: it is permitted by local laws and regulations; the ethics committee is, in principle, in agreement; and the investigator thinks that participation will promote the welfare and be in the interest of the subject. The agreement of a legally acceptable representative that participation will promote the welfare and be in the interest of the subject should also be recorded by a dated signature. If the patient is incapable of giving either signed informed consent or witnessed signed verbal consent, this fact must be documented by the investigator, stating the reasons.

g) In a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her signature.

h) The trial subjects should be informed that they have access to appropriate (identified) persons to obtain further information and medical advice or escape treatment, if necessary.

i) Any information that becomes available during the trial which may be of relevance to the trial subjects must be made known to them by the investigator.

j) The subjects should be informed of the circumstances under which the investigator or the sponsor might terminate their participation in the study.

3.4 *Confidentiality*

The investigator must establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2)*. (See also Section 3.3.)

4. RESPONSIBILITIES OF THE INVESTIGATOR

4.1 *Medical care of trial subjects*

The investigator is responsible for adequate and safe medical care (or dental care, where appropriate) of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 *Qualifications*

The investigator should:

- have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials (decisions relating to, and provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practice medicine or dentistry);
- have good knowledge and experience of the field of medicine/dentistry defined by the protocol;
- be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
- be aware of available relevant data and literature and all information provided by the sponsor;
- have access to human and other resources to assume full responsibility for the proper conduct of the trial;
- be aware of and comply with national regulatory, legal and ethical requirements.

4.3 *Selection of trial subjects*

The investigator is responsible for ensuring the unbiased selection and an adequate number of suitable subjects according to the protocol. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects.

In order to assess the probability of recruiting an adequate number of subjects for the study, it may be useful to determine prospectively or to review retrospectively (e.g. on the basis of the clinic's records) the availability of potential subjects. The investigator should check whether subjects so identified can or could be included according to protocol.

The patient's own physician should, when relevant and with the patient's consent, be informed of the patient's participation in the clinical trial.

4.4 *Compliance with the protocol*

The investigator must agree and sign the protocol (or another legally acceptable document mentioning the agreement with the protocol) with the sponsor, and confirm in writing that he or she has read, understands and will work according to the protocol and Good Clinical Practice.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and the sponsor. Amendments which are likely to affect the safety of a subject or the conduct of the clinical trial should be submitted in writing to the ethics committee (see Section 3.2) and drug regulatory authority and implemented only after approval has been received.

The investigator may take any steps judged necessary to protect the safety of the trial subject, whether specified in the protocol or not. Any such steps must be documented.

4.5 *Information for subjects and informed consent*

The investigator is responsible for giving adequate information to subjects about the trial. The current version of the Declaration of Helsinki (Appendix 1), and International Ethical Guidelines for Biomedical Research Involving Human Subjects(2) should be followed. The nature of the investigational pharmaceutical product, its stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Information should be given in both oral and written form in a language understandable to the subject. The protocol should state when and by whom such information will be provided, and how the provision of information should be recorded.

Informed consent must be obtained according to the principles described in Section 3.3.

The investigator should also supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact person(s) to contact in an emergency situation.

4.6 *The investigational product*

The investigator must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product(s), including pre-trial data, as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the clinical trial.

4.7 *Site of the trial, facilities and staff*

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

The investigator should ensure that he or she has sufficient time to conduct and complete the trial, and that other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand.

The investigator must provide adequate information to all staff involved in the trial.

The investigator must notify or obtain approval for the trial from relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 *Notification of the trial or submission to the drug regulatory authority*

As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor, should give notification of the trial to, or obtain approval from, the drug regulatory authority. Any submission to the drug regulatory authority should be in writing and dated, and contain sufficient information to identify the protocol.

4.9 *Review by an ethics committee*

Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s) (see Section 3.2). Any submission to and acceptance by the ethics committee should be in writing and dated, and contain sufficient information to identify the protocol or other submitted documents.

4.10 *Serious adverse events/reactions*

The investigator must take appropriate measures to ensure the safety of clinical trial subjects (see also Section 7). The investigator is also responsible for notifying (with documentation) the relevant health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events or reactions, as governed by national regulations.

4.11 *Financing*

The relationship between the investigator and the sponsor in matters such as financial support, fees, honorarium payments in kind must be stated in writing in the protocol or contract. The protocol or contract should be available to the drug regulatory authority and ethics committee on demand.

4.12 *Monitoring, auditing and inspection*

The investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits (see also Section 6). In addition, the investigator must accept auditing and/or inspection by the relevant health authorities and by persons appointed by the sponsor for quality assurance.

4.13 *Record-keeping and handling of data*

See Section 8.

4.14 *Handling of and accountability for pharmaceutical products for trial*

See Section 10.

4.15 *Termination of trial*

In the case of premature termination of the clinical trial, the investigator must inform the drug regulatory authority, the ethics committee and, where applicable, the sponsor. Reasons for termination must be stated in writing.

4.16 *Final report*

After completion of the trial, a final report must be drawn up and submitted to the drug regulatory authority. The report should be dated and signed by the investigator in accordance with local regulations to verify responsibility for the validity of the data.

4.17 *Trials in which the investigator is the sponsor*

In clinical trials in which the investigator is the sponsor, he or she is responsible for the corresponding functions (see Section 5).

5. RESPONSIBILITIES OF THE SPONSOR

The sponsor is often a pharmaceutical company, but may also be an individual, the investigator, or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a clinical trial. When the sponsor is a foreign company or organization it should have a local representative to fulfil the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for providing the investigational and comparator (if any) products, as well as appropriate information to support the safe use of those products. In addition, the sponsor is responsible for ensuring that the trial is conducted in accordance with sound scientific principles and Good Clinical Practice standards by selecting qualified investigators, providing a protocol and ensuring protocol compliance, establishing the distribution of trial-related responsibilities, and providing facilities, equipment and staff for management of the trial, record-keeping, handling of data, monitoring, and quality assurance. The sponsor is also ultimately responsible for ensuring compliance with applicable legal, ethical, and regulatory requirements (although local regulations may designate certain required activities as responsibilities of the investigator), and for providing compensation and indemnity in the event of trial-related injury or death, according to local laws and regulations.

5.1 *Selection of the investigator(s)*

The sponsor is responsible for selecting the investigator(s), taking into account the appropriateness and availability of the trial site and facilities, and being assured of the investigator's qualifications and availability to conduct the study.

5.2 *Delegation of responsibilities*

The sponsor is responsible for agreeing with the investigator(s) on the allocation of protocol-related responsibilities, including data processing, breaking of the trial code, handling of statistics, preparation of trial reports, and preparation and submission of documentation to the ethics committee, the drug regulatory authority, and any other required review bodies. This agreement should be confirmed in writing (protocol, contract, or alternative document) prior to the trial.

The sponsor may transfer any or all clinical trial-related activities to a scientific body (commercial, academic, or other), or to a contract research organization (CRO). Any such transfer should be documented in writing.

5.3 *Compliance with the protocol and procedures*

The sponsor is responsible for assuring the investigator's agreement to undertake the clinical trial as described in the protocol, and according to Good Clinical Practice, and to accept procedures for data recording (particularly in the case-report form or CRF), monitoring, audits, and inspections. The sponsor and the investigator must sign the protocol or an alternative document confirming this agreement.

Both the sponsor and the investigator should agree to any amendment to the protocol before it is implemented and this should be documented in writing.

Amendments which may affect the safety of the subjects or the conduct of the trial should be submitted in writing to the ethics committee (see Section 3.2) through the investigator or, if applicable, directly by the sponsor. The sponsor should provide justification for the amendments. If required, the amendments should be submitted to the drug regulatory authority. The amendments should not be implemented until all required approvals have been obtained, unless the delay caused by this process is likely to expose the subjects to an immediate hazard or danger.

5.4 *Product information*

As a prerequisite to planning the clinical trial, the sponsor is responsible for providing the investigator with available chemical/pharmaceutical, toxicological, pharmacological and clinical data (including data from previous and ongoing trials) regarding the investigational product and, where appropriate, the comparator product(s). This information should be accurate and adequate to justify the nature, scale and duration of the trial. In addition, the sponsor must bring any relevant new information arising during the trial to the attention of the investigator.

The sponsor is responsible for preparing and providing to investigators an Investigator's brochure, which must include all relevant information about the product(s) and must be supplemented and/or updated whenever any relevant new information is available.

5.5 *Safety information*

The sponsor must inform the investigator(s) promptly of any immediately relevant information on safety that becomes available during a clinical trial and ensure that the ethics committee and the drug regulatory authority are notified by the investigator(s) if required (see Section 7).

5.6 *Investigational product*

The sponsor is responsible for supplying the investigational pharmaceutical product(s) and, if applicable, comparator products, prepared in accordance with principles of Good Manufacturing Practice (GMP) (see also Section 10). The product(s) should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration and safeguard blinding procedures (if applicable); appropriate investigational labelling should be affixed.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that, if necessary, an independent laboratory is able to re-check the investigational product(s), e.g. for quality control or bioequivalence.

Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch or serial numbers. The sponsor must ensure that the investigator is able to establish a system within his or her institution for adequate and safe handling, storage, use, return (to the investigator or sponsor) and, if appropriate, destruction of the investigational product(s).

5.7 *Trial management and handling of data*

The sponsor should appoint appropriate individuals and/or committees for managing and supervising the clinical trial, handling and verifying the data obtained, statistical processing, and preparing the trial report (see Section 8).

5.8 *Standard operating procedures*

Where warranted by the number or scale of clinical trials conducted, it is recommended that the sponsor establish written standard operating procedures (SOP) to comply with Good Clinical Practice.

5.9 *Compensation to subjects and investigators*

As required by national law or regulations, the sponsor should provide adequate compensation or treatment for subjects in the event of trial-related injury or death, and provide indemnity for the investigator, except in the case of claims resulting from malpractice and/or negligence. (See Section 3.2 e–f).

5.10 *Monitoring*

The sponsor must appoint suitable and appropriately trained monitors and clinical research support personnel, and provide ongoing training to ensure that they are suitably qualified an to keep them up to date with new developments.

5.11 *Quality assurance*

The sponsor should establish a system or systems of quality assurance (including independent auditing) to ensure that the conduct of the clinical trial and the generation, documentation, and reporting of data comply with the protocol, Good Clinical Practice standards and applicable regulatory requirements. The system should operate independently of those involved in conducting or monitoring the trial (see Section 12).

5.12 *Study reports*

The sponsor is responsible for ensuring the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory purposes, whether or not the trial has been completed. The sponsor must also submit any relevant safety information (including safety) that becomes available during the trial and/or annual reports as required by the relevant health authorities.

5.13 *Handling of adverse events*

The sponsor should provide special forms for reporting any adverse event that occur during the clinical trial. The sponsor must investigate promptly, together with the investigator(s), all serious adverse events, take appropriate measures to ensure the safety of trial subjects, and report these events to appropriate authorities in accordance with applicable national requirements (see Section 7).

5.14 *Termination of trial*

If the sponsor elects or is required to terminate the clinical trial prematurely, then the investigator(s), ethics committee and relevant authorities must be notified of this decision, and of the reasons for termination.

6. RESPONSIBILITIES OF THE MONITOR

The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

The main responsibility of the monitor is to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements. The monitor is responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly to the sponsor and the relevant ethics committee(s).

The monitor should follow a predetermined written set of standard operating procedures (SOP). A written record should be kept of all visits, telephone calls and letters to the investigator.

6.1 *Qualifications*

The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical, and/or scientific qualifications, and clinical trial experience. The qualifications most appropriate for a monitor will depend on the type of trial and nature of the product under investigation.

6.2 *Assessment of the trial site*

The monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an adequate number of trial

subjects is likely to be available for the duration of the trial. The monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of standard operating procedures (SOP).

6.3 *Staff education and compliance*

The monitor should ensure that all staff assisting the investigator in the trial have been adequately informed about and will comply with the details of the trial protocol.

6.4 *Data management*

The monitor should assist the investigator in reporting the data and results of the trial to the sponsor, e.g. by providing guidance on correct procedures for completion of case-report forms (CRFs), and by verifying the accuracy of data obtained (see also Section 8).

6.5 *Case-report forms*

The monitor is responsible for ensuring that all case-report forms (CRFs) are correctly filled out in accordance with original observations. Any errors or omissions should be clarified with the investigator, corrected, and explained on the CRF. Procedures should be established for the investigator's certification of the accuracy of CRFs by a signature, initials or similar method. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the clinical trial.

6.6 *Investigational product*

The monitor should confirm that procedures for the storage, dispensing, and return of investigational product(s) are safe, adequate, and properly documented in accordance with local regulations and the trial protocol (see also Section 10.4).

6.7 *Communication*

The monitor should facilitate communication between the investigator and sponsor. The monitor (or some other responsible person designated by the sponsor and known to the investigator) should be available to the investigator at all times for reporting of adverse events or consultation on other trial-related matters.

6.8 Notification of the trial or submission to the drug regulatory authority

The monitor should assist the investigator in notifying the drug regulatory authority of the clinical trial and submitting any necessary documentation.

6.9 *Reports*

The monitor should submit a written monitor report to the sponsor after each site visit and after all relevant telephone calls, letters and other contacts with the investigator. The report should include details of the findings and any actions taken.

7. MONITORING OF SAFETY

7.1 *Handling of and recording adverse events*

In accordance with Sections 4.1 and 4.3 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality.

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the clinical trial.

The trial protocol should clearly state the method(s) by which adverse events will be monitored. Provisions should be included to ensure prompt dose reduction or withdrawal of therapy for patients experiencing unacceptable toxic effects. The protocol should describe how information relating to adverse events is to be handled and analysed by the investigator and sponsor, and their responsibilities to report to each other and to the drug regulatory authority. The sponsor should provide special forms for reporting trial-related adverse events.

Consideration should be given to establishing a special committee to monitor adverse events (see also Section 13).

7.2 Reporting

Regulations

National regulations vary considerably in their requirements for reporting of adverse events. For serious events, however, accelerated reporting is required.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events or reactions (e.g. serious, previously unknown) to the drug regulatory authority and the ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the trial and on the future use of the product. In reporting, measures should be taken to avoid unnecessary duplication.

The investigator

The investigator has to report serious adverse events to the sponsor immediately and to the drug regulatory authority and the ethics committee as specified in the protocol and in accordance with national regulations. Normally, adverse events associated with the use of the product must be reported to the drug regulatory authority within a specified time limit.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (i.e. the unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code to facilitate data verification by the sponsor or drug regulatory authority and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events should be stated.

After the trial has been completed or terminated, all recorded adverse events should be listed, evaluated and discussed in the final report.

The sponsor

During the trial, the sponsor is responsible for reporting and trial-related adverse events or reactions associated with the use of the investigational product to the local health authority as required by national regulations and to other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as to the drug regulatory authority and relevant authorities in other countries any trial with the same product that has been stopped due to action taken by a regulatory authority, or any other withdrawals of the product from the market for safety reasons. The sponsor should amend the investigator's

brochure as required to keep the description of adverse events updated and to include any other significant new safety information.

8. RECORD KEEPING AND HANDLING OF DATA

The aim of record-keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately, the information gathered on each trial subject into data that can be used in the report.

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of quality of the data and the performance of the clinical trial (the "audit paper trail" concept). Documentation is facilitated by methods such as the use of check-lists and forms giving details of action taken, dates, the individuals responsible, etc.

The allocation of responsibilities for record-keeping and handling of data should be specified in the protocol or other written agreement(s) between the sponsor and investigator(s).
A basic aspect of the integrity of data is the safeguarding of "blinding" with regard to treatment assignment. It starts with the randomization of patients into treatment groups and is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic data handling, confidentiality of the database must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance of the database and for back-up procedures.

8.1 *Responsibilities of the investigator*

a) The investigator has overall responsibility for ensuring the accuracy and completeness of data entry. The investigator must ensure that the observations and findings are recorded correctly and completely in the case-report forms (CRFs) and signed by the responsible person designated in the protocol.
When conducting a study and using CRFs to report clinical trial data to the sponsor, the investigator must also ensure that the routine requirements for recording of data in the source documents (e.g. hospital and laboratory records, consultation files) are met, particularly those relating to the treatment given to the subject and adverse events.

b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated print-out and back-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

c) All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented.

d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.

e) Data other than those required by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.

f) Units of measurement must always be stated, and conversion of units must always be indicated and documented.

g) The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s) as well as the responsible statistician, in accordance with the applicable regulations.
h) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual subjects in the trial (subject identification code). The investigator may submit the subject identification code list to the drug regulatory authority after the trial, together with the final report, according to national regulations.
i) The investigator should ensure that the subject's participation in the clinical trial is clearly marked in his or her medical records.

8.2 *Responsibilities of the sponsor and the monitor*

a) When electronic data handling or remote electronic data entry systems are employed, the sponsor must use validated, data processing programs with adequate user documentation. A predetermined set of standard operating procedures (SOP) for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file.

b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns values automatically when data are missing, this should be made clear.

c) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data printout with the original observations and findings.

d) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.

e) The sponsor must maintain a list of persons authorized to make corrections, and prevent unauthorized access to the data by appropriate security systems.

8.3 *Archiving of data*

As required by national regulations, the investigator must arrange for the retention of the subject identification codes for a sufficient period of time to permit any medical follow-up which may be warranted, including follow-up for delayed toxic reactions. It must be possible to identify each trial subject by name against subject and product container identification codes, treatment assignment, and the CRFs. Subject files and other supporting data must be kept for a period of time required by local regulations. The sponsor or supplier of the product must make appropriate arrangements for the retention of all other essential documentation pertaining to the clinical trial in a form which can be retrieved for future reference. Archived data may be kept on microfiche or electronic or optical record (e.g. compact disc), provided that a hard copy can be made available on request.

The protocol, documentation, approvals and all other essential documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. STATISTICS AND CALCULATIONS

The use of qualified biostatistical expertise is necessary before and throughout the entire clinical trial procedure, commencing with the design of the protocol and case-report forms (CRFs) and ending with the completion of the final report and/or publication of the results.

The sponsor and the investigator should agree where and by whom the statistical work should be carried out. This information and the name of the responsible statistician should be recorded in the protocol.

9.1 *Experimental design*

The scientific integrity of a clinical trial and the credibility of the data produced depend primarily on the design of the trial. In the case of comparative trials, the protocol should therefore describe:

- an *a priori* rationale for the targeted difference between treatments that the trial is designed to detect, and the statistical power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences;
- measures taken to avoid bias, particularly with regard to the randomization, when relevant, and selection of patients.

9.2 *Randomization and blinding*

In case of a randomized clinical trial, the randomization procedure must be documented. Where a sealed code for each individual treatment has been supplied in a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial the protocol must state the conditions under which the code is allowed to be broken and by whom. A system is also required to enable immediate access to the information about treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, this must be justified and documented in the CRF.

9.3 *Statistical analysis*

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be justified and described in the final report of the clinical trial. The statistical analysis should be planned and carried out or verified by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and the monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of statistical analyses should be presented in such a manner as to facilitate interpretation of their clinical importance, e.g. as estimates of the magnitude of the treatment effect, the difference between treatments and confidence intervals, rather than in a form that relies solely on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The sponsor is responsible for ensuring that the investigational pharmaceutical product(s) and, if applicable, comparator products supplied for the clinical trial are of appropriate quality and subject to quality assurance procedures (see Section 5.11).

If significant changes are made in the formulation of the investigational or comparator product during the course of the trial, the results of additional studies (e.g. on the stability, comparative dissolution rate or, as appropriate, comparative bioavailability) should be made available before the new formulation is used in the trial. The studies would demonstrate that the changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product.

10.1 *Supply and storage*

The arrangements made by the sponsor to supply the investigator with pharmaceutical products for the trial should be described in the protocol. The manner in which study products are to be recorded, delivered, dispensed and stored should be detailed.

The principles of Good Manufacturing Practice*(1)* should be applied not only by the supplier of the pharmaceutical product(s), but also by any intermediaries responsible for storing the product(s) temporarily.

Records must be kept of information about the shipment, delivery, receipt, storage, return and destruction of any remaining pharmaceutical products. The investigator should not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the local hospital should assume responsibility for storage, delivery, return and keeping records of the investigational and, when appropriate, comparator product(s). If so, these procedures must be documented to make auditing possible.

10.2 *Investigational labelling and packaging*

The sponsor is responsible for the proper packaging and investigational labelling of the pharmaceutical products used. Study products should be labelled in compliance with the protocol and any applicable national regulations. The investigational label should state that the product is for clinical research purposes only. Investigational label information should be accurate and in a language that is understandable to the subject.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. A coding system should be used to allow for the proper identification of the blinded products given to individual subjects (in case of emergency). In addition, all study products, including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

10.3 *Responsibilities of the investigator*

The investigator is responsible for ensuring:

- Proper and safe handling of the investigational and, when appropriate, comparator products during and after the clinical trial, preferably in cooperation with a pharmacy (see Section 10.1);
- That the investigational product is used only in accordance with the protocol, which implies use only for subjects included in the trial and by designated staff responsible to the investigator, and that this use is documented in such a way as to ensure appropriate dosage;
- That the dosage and instructions for use are correct and that every subject involved understands them properly;
- That unused investigational and, when appropriate, comparator products are returned in accordance with the protocol to the pharmacy or sponsor or destroyed, and that proper records of these activities are kept.

10.4 *Responsibilities of the sponsor and monitor (see also Sections 5 and 6)*

The sponsor is responsible for:

- Supplying the investigational and, when appropriate, comparator product(s), prepared in accordance with principles of Good Manufacturing Practice. The products should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration during transport and storage at intermediate destinations; appropriate investigational labelling should be affixed (see Section 10.2).
- Ensuring that the package of investigational product(s) is of a size suitable for the trial and adequate for the trial subjects.
- Keeping sufficient samples from each batch used in the trial as a reference for control tests and validation of data, as required in national regulations.
- Providing information about the expiry date (month/year) or retest date information in a manner understandable to all staff involved in the trial.

During the visits to the clinical trial site, the monitor should check:

- That all study products for the trial are used exclusively within the limits defined by the protocol.
- That inventory records of study products are in order and that there are sufficient supplies.
- That the expiry dates are not likely to be, or have not been, exceeded.
- That the storage conditions for study products are adequate.
- Procedures for and records of returned and/or unused study products.

11. ROLE OF THE DRUG REGULATORY AUTHORITY

The role of governments is to provide the legal framework for clinical trials. The aim should be twofold: (i) to protect the safety and rights of the subjects participating in a trial, and (ii) to ensure that trials are adequately designed to meet scientifically sound objectives. These aims may be met by several means, including the specification of the investigator's qualifications and requirement for review and approval of the protocol by relevant scientific and/or ethics committees.

Drug regulatory authorities should have a mandate to review protocols and, where necessary, to protect the safety of subjects, to require protocol revisions and/or termination of trials.

Regulations should allow for on-site inspections of the quality and reliability of the data obtained, with due concern for confidentiality.

11.1 *General responsibilities*

The national drug regulatory authority should ensure that the protocols for clinical trials are submitted in advance for review and are in accordance with existing national regulations. On the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions or request additional data on a clinical trial or terminate a trial.

The drug regulatory authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor (see Section 6.9). In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

National regulations should specify the procedures for reporting and handling cases of misconduct discovered in connection with clinical trials.

11.2 *On-site inspections*

As permitted by national regulations, the drug regulatory authority may carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the drug regulatory authority by the investigator or the sponsor.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for ease of retrieval.

Inspections may include data audit. The drug regulatory authority should have easy access to all patient files and raw data used for and generated during the trial.

12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The sponsor is responsible for implementing a system of quality assurance in order to ensure that the trial is performed and the data are generated, recorded, and reported in compliance with the protocol, Good Clinical Practice, and national regulations.

All clinical trial sites, data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. The verification processes must be specified and scientifically justified. Statistically controlled sampling may be used to verify data in a trial.

Quality control procedures must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor, investigational sites, facilities and laboratories, and all relevant data (including raw data) and documentation and reports concerning the data (including subject files) must be available for an audit and for inspection by relevant health authorities. The audit should be conducted by a nominated person(s) or organization(s) independent of those carrying out the clinical trial.

13. CONSIDERATIONS FOR MULTICENTRE TRIALS

Because a multicentre trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multi-centre trials, such as:

- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- the submission of the proposed protocol or protocol amendments to the ethics committee(s), and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved in the trial;
- implementation of the trial;
- the procedures used for the randomization of trial subjects;

ensuring that the quality of the product is maintained during distribution and storage in different locations;
the training of investigators to follow the same protocol;
standardization of methods for evaluating and analysing laboratory and diagnostic data (e.g. establishment of an external quality control system for laboratory assays);
control of adherence to the protocol, including measures to terminate participation of trial sites if necessary;
the role of the monitor(s);
centralized data management and analysis;
drafting of the final report and clearances required;
publication of the trial results.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and knowledge of the investigational pharmaceutical product. One or several committees may be set up for this purpose or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or person(s) should be described in the trial protocol, as should the procedure for nomination.

For example, a committee or an individual could be responsible for overseeing the initiation overall performance of the trial. Similarly, a second committee or person could be appointed to provide advice on policy matters and data collection. A third committee or person could be made responsible to the accuracy and verification of the data obtained. It should be stated in the protocol under what circumstances and how this committee or person can break the trial code. Collaboration between these committee(s) or person(s) is necessary.

A coordinating committee could also be set up or a coordinator appointed with responsibility for the control of the performance and progress of the trial and maintaining contacts with the drug regulatory authorities and ethics committees.

These administrative arrangements will provide adequate assurance that the study will be planned and conducted according to generally accepted scientific principles and Good Clinical Practice.

References

1. Good manufacturing practices for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-second report, Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), annex 1.

2. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, CIOMS, 1993, Annex 1.

Declaration of Helsinki**

Recommendations guiding physicians in biomedical research involving human subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a

physician who Is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental designed is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

***Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989. World Medical Association, Handbook of declarations, Ferney-Voltaire 1992 (unpublished document; available on request from the World Medical Association, 28 avenue des Alpes, 01210 Ferney-Voltaire, France). [Internet address:* http://www.wma.net/*]*

APPENDIX 2

MODEL LIST OF ITEMS TO BE CONTAINED IN A CLINICAL TRIAL PROTOCOL

The trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.

2. Statement of rationale, objectives and purpose of trial.

3. Brief description of the site(s) where the trial is to be conducted

4. Name and address of the sponsor.

5. Name, address and qualifications of each investigator.

6. Description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), and method of and procedure(s) for randomization.

7. Description of trial subjects (criteria for inclusion and exclusion of potential subjects), process of recruitment, types, method(s) and timing of allocation of subjects into investigational groups.

8. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.

9. Description of and justification for the route of administration, dosage, dosage interval and treatment period for the investigational and comparator products, if used. Dose-response relationships should be considered.

10. Any other treatment that may be given or permitted concomitantly.

11. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.

12. Description of how responses are recorded (description and evaluation of methods and frequency of measurement), follow-up procedures and measures to determine the extent of compliance with the treatment among trial subjects.

13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.

14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.

15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case-report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency.

17. Measures to be implemented to ensure the safe handling and storage of investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.

18. Description of methodology to be used to evaluate the results, (including statistical methods) and to report on patients or participants withdrawn from the trial.

19. Time schedule for completion of the trial.

20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.

21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

22. Ethical considerations and measures relating to the trial.

23. Medical care to be provided after the trial, modalities of post-trial treatment.

24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.

25. List of literature referred to in the protocol.

TDR/PRD/ETHICS/2000.1

Operational Guidelines for Ethics Committees That Review Biomedical Research

World Health Organization
Geneva
2000

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means – electronic, mechanical or other – without the prior written permission of WHO.

The views expressed in documents by named authors, are solely the responsibility of those authors.

© World Health Organization 2000

TABLE OF CONTENTS

PREFACE ..... *v*

1 OBJECTIVE 1

2 THE ROLE OF AN EC 1

3 ESTABLISHING A SYSTEM OF ETHICAL REVIEW 2

4 CONSTITUTING AN EC 2

4.1 Membership Requirements *3*

4.2 Terms of Appointment *4*

4.3 Conditions of Appointment *4*

4.4 Offices *5*

4.5 Quorum Requirements *5*

4.6 Independent Consultants *5*

4.7 Education for EC Members *6*

5 SUBMITTING AN APPLICATION 6

5.1 Application *6*

5.2 Application Requirements *6*

5.3 Documentation *7*

6 REVIEW 9

6.1 Meeting Requirements *9*

6.2 Elements of the Review *10*

6.3 Expedited Review *13*

7 DECISION-MAKING 14

8 COMMUNICATING A DECISION 15

9 FOLLOW-UP 16

10 DOCUMENTATION AND ARCHIVING 18

GLOSSARY 21

SUPPORTING DOCUMENTS 23

COMMITTEES 25

BACKGROUND 29

PREFACE

The ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the WHO and ICH Guidelines for Good Clinical Practice. Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well-being of research participants are promoted and that the results of the investigations are credible.

All international guidelines require the ethical and scientific review of biomedical research alongside informed consent and the appropriate protection of those unable to consent as essential measures to protect the individual person and the communities who participate in research. For the purposes of these Guidelines, biomedical research includes research on pharmaceuticals, medical devices, medical radiation and imaging, surgical procedures, medical records, and biological samples, as well as epidemiological, social, and psychological investigations.

These Guidelines are intended to facilitate and support ethical review in all countries around the world. They are based on a close examination of the requirements for ethical review as established in international guidelines, as well as on an evaluation of existing practices of ethical review in countries around the world. They do not, however, purport to replace the need for national and local guidelines for the ethical review of biomedical research, nor do they intend to supersede national laws and regulations.

The majority of biomedical research has been predominantly motivated by concern for the benefit of already privileged communities. This is reflected by the fact that the WHO estimates that 90% of the resources devoted to research and development on medical problems are applied to diseases causing less than 10% of the present global suffering. The establishment of international guidelines that assist in strengthening the capacity for the ethical review of biomedical research in all countries contributes to redressing this imbalance.

1 OBJECTIVE

The objective of these Guidelines is to contribute to the development of quality and consistency in the ethical review of biomedical research. The Guidelines are intended to complement existing laws, regulations, and practices, and to serve as a basis upon which ethics committees (ECs) can develop their own specific written procedures for their functions in biomedical research. In this regard, the Guidelines establish an international standard for ensuring quality in ethical review. The Guidelines should be used by national and local bodies in developing, evaluating, and progressively refining standard operating procedures for the ethical review of biomedical research.

2 THE ROLE OF AN EC

The purpose of an EC in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants. A cardinal principle of research involving human participants is 'respect for the dignity of persons'. The goals of research, while important, should never be permitted to override the health, well-being, and care of research participants. ECs should also take into consideration the principle of justice. Justice requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture, and ethnic considerations.

ECs should provide independent, competent, and timely review of the ethics of proposed studies. In their composition, procedures, and decision-making, ECs need to have independence from political, institutional, professional, and market influences. They need similarly to demonstrate competence and efficiency in their work.

ECs are responsible for carrying out the review of proposed research before the commencement of the research. They also need to ensure that there is regular evaluation of the ethics of ongoing studies that received a positive decision.

ECs are responsible for acting in the full interest of potential research participants and concerned communities, taking into account the interests and needs of the researchers, and having due regard for the requirements of relevant regulatory agencies and applicable laws.

3 ESTABLISHING A SYSTEM OF ETHICAL REVIEW

Countries, institutions, and communities should strive to develop ECs and ethical review systems that ensure the broadest possible coverage of protection for potential research participants and contribute to the highest attainable quality in the science and ethics of biomedical research. States should promote, as appropriate, the establishment of ECs at the national, institutional, and local levels that are independent, multi-disciplinary, multi-sectorial, and pluralistic in nature. ECs require administrative and financial support.

Procedures need to be established for relating various levels of review in order to ensure consistency and facilitate cooperation. Mechanism for cooperation and communication need to be developed between national committees and institutional and local committees. These mechanisms should ensure clear and efficient communication. They should also promote the development of ethical review within a country as well as the ongoing education of members of ethics committees. In addition, procedures need to be established for the review of biomedical research protocols carried out at more than one site in a country or in more than one country. A network of ethical review should be established at the regional, national, and local levels that ensures the highest competence in biomedical review while also guaranteeing input from all levels of the community.

4 CONSTITUTING AN EC

ECs should be constituted to ensure the competent review and evaluation of all ethical aspects of the research projects they receive and

to ensure that their tasks can be executed free from bias and influence that could affect their independence.

ECs should be multidisciplinary and multi-sectorial in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community.

ECs should be established in accordance with the applicable laws and regulations of the country and in accordance with the values and principles of the communities they serve.

ECs should establish publicly available standard operating procedures that state the authority under which the committee is established, the functions and duties of the EC, membership requirements, the terms of appointment, the conditions of appointment, the offices, the structure of the secretariat, internal procedures, and the quorum requirements. ECs should act in accordance with their written operating procedures.

It may be helpful to summarize the activities of the EC in a regular (annual) report.

4.1 Membership Requirements

Clear procedures for identifying or recruiting potential EC members should be established. A statement should be drawn up of the requirements for candidacy that includes an outline of the duties and responsibilities of EC members.

Membership requirements should be established that include the following:

4.1.1 the name or description of the party responsible for making appointments;

4.1.2 the procedure for selecting members, including the method for appointing a member (e.g., by consensus, by majority vote, by direct appointment);

4.1.3 conflicts of interest should be avoided when making appointments, but where unavoidable there should be transparency with regard to such interests.

A rotation system for membership should be considered that allows for continuity, the development and maintenance of expertise within the EC, and the regular input of fresh ideas and approaches.

4.2 Terms of Appointment

Terms of appointment should be established that include the following:

4.2.1 the duration of an appointment,

4.2.2 the policy for the renewal of an appointment,

4.2.3 the disqualification procedure,

4.2.4 the resignation procedure,

4.2.5 the replacement procedure.

4.3 Conditions of Appointment

A statement of the conditions of appointment should be drawn up that includes the following:

4.3.1 a member should be willing to publicize his/her full name, profession, and affiliation;

4.3.2 all reimbursement for work and expenses, if any, within or related to an EC should be recorded and made available to the public upon request;

4.3.3 a member should sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; in addition, all EC administrative staff should sign a similar confidentiality agreement.

4.4 Offices

ECs should establish clearly defined offices for the good functioning of ethical review. A statement is required of the officers within the EC (e.g., chairperson, secretary), the requirements for holding each office, the terms and conditions of each office, and the duties and responsibilities of each office (e.g., agenda, minutes, notification of decisions). Clear procedures for selecting or appointing officers should be established.

In addition to the EC officers, an EC should have adequate support staff for carrying out its responsibilities.

4.5 Quorum Requirements

ECs should establish specific quorum requirements for reviewing and deciding on an application. These requirements should include:

4.5.1 the minimum number of members required to compose a quorum (e.g., more than half the members);

4.5.2 the professional qualifications requirements (e.g., physician, lawyer, statistician, paramedical, layperson) and the distribution of those requirements over the quorum; no quorum should consist entirely of members of one profession or one gender; a quorum should include at least one member whose primary area of expertise is in a non-scientific area, and at least one member who is independent of the institution/research site.

4.6 Independent Consultants

ECs may call upon, or establish a standing list of, independent consultants who may provide special expertise to the EC on proposed research protocols. These consultants may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities, patients, or special interest groups. Terms of reference for independent consultants should be established.

4.7 Education for EC Members

EC members have a need for initial and continued education regarding the ethics and science of biomedical research. The conditions of appointment should state the provisions available for EC members to receive introductory training in the work of an EC as well as ongoing opportunities for enhancing their capacity for ethical review. These conditions should also include the requirements or expectations regarding the initial and continuing education of EC members. This education may be linked to co-operative arrangements with other ECs in the area, the country, and the region, as well as other opportunities for the initial and continued training of EC members.

5 SUBMITTING AN APPLICATION

ECs are responsible for establishing well-defined requirements for submitting an application for review of a biomedical research project. These requirements should be readily available to prospective applicants.

5.1 Application

An application for review of the ethics of proposed biomedical research should be submitted by a qualified researcher responsible for the ethical and scientific conduct of the research.

5.2 Application Requirements

The requirements for the submission of a research project for ethical review should be clearly described in an application procedure. These requirements should include the following:

5.2.1 the name(s) and address(es) of the EC secretariat or member(s) to whom the application material is to be submitted;

5.2.2 the application form(s);

5.2.3 the format for submission;

5.2.4 the documentation (see 5.3);

5.2.5 the language(s) in which (core) documents are to be submitted;

5.2.6 the number of copies to be submitted;

5.2.7 the deadlines for submission of the application in relation to review dates;

5.2.8 the means by which applications will be acknowledged, including the communication of the incompleteness of an application;

5.2.9 the expected time for notification of the decision following review;

5.2.10 the time frame to be followed in cases where the EC requests supplementary information or changes to documents from the applicant;

5.2.11 the fee structure, if any, for reviewing an application;

5.2.12 the application procedure for amendments to the protocol, the recruitment material, the potential research participant information, or the informed consent form.

5.3 Documentation

All documentation required for a thorough and complete review of the ethics of proposed research should be submitted by the applicant. This may include, but is not limited to,

5.3.1 signed and dated application form;

5.3.2 the protocol of the proposed research (clearly identified and dated), together with supporting documents and annexes;

5.3.3 a summary (as far as possible in non-technical language),

synopsis, or diagrammatic representation ('flowchart') of the protocol;

5.3.4 a description (usually included in the protocol) of the ethical considerations involved in the research;

5.3.5 case report forms, diary cards, and other questionnaires intended for research participants;

5.3.6 when the research involves a study product (such as a pharmaceutical or device under investigation), an adequate summary of all safety, pharmacological, pharmaceutical, and toxicological data available on the study product, together with a summary of clinical experience with the study product to date (e.g., recent investigator's brochure, published data, a summary of the product's characteristics);

5.3.7 investigator(s)'s curriculum vitae (updated, signed, and dated);

5.3.8 material to be used (including advertisements) for the recruitment of potential research participants;

5.3.9 a description of the process used to obtain and document consent;

5.3.10 written and other forms of information for potential research participants (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages;

5.3.11 informed consent form (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages;

5.3.12 a statement describing any compensation for study participation (including expenses and access to medical care) to be given to research participants;

5.3.13 a description of the arrangements for indemnity, if applicable;

5.3.14 a description of the arrangements for insurance coverage for research participants, if applicable;

5.3.15 a statement of agreement to comply with ethical principles set out in relevant guidelines;

5.3.16 all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of modification(s) to the protocol made on that account. The reasons for previous negative decisions should be provided.

6 REVIEW

All properly submitted applications should be reviewed in a timely fashion and according to an established review procedure.

6.1 Meeting Requirements

ECs should meet regularly on scheduled dates that are announced in advance. The meeting requirements should include the following:

6.1.1 meetings should be planned in accordance with the needs of the workload;

6.1.2 EC members should be given enough time in advance of the meeting to review the relevant documents;

6.1.3 meetings should be minuted; there should be an approval procedure for the minutes;

6.1.4 the applicant, sponsor, and/or investigator may be invited to present the proposal or elaborate on specific issues;

6.1.5 independent consultants may be invited to the meeting or to provide written comments, subject to applicable confidentiality agreements.

6.2 Elements of the Review

The primary task of an EC lies in the review of research proposals and their supporting documents, with special attention given to the informed consent process, documentation, and the suitability and feasibility of the protocol. ECs need to take into account prior scientific reviews, if any, and the requirements of applicable laws and regulations. The following should be considered, as applicable:

6.2.1 Scientific Design and Conduct of the Study

6.2.1.1 the appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation), and the potential for reaching sound conclusions with the smallest number of research participants;

6.2.1.2 the justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities;

6.2.1.3 the justification for the use of control arms;

6.2.1.4 criteria for prematurely withdrawing research participants;

6.2.1.5 criteria for suspending or terminating the research as a whole;

6.2.1.6 the adequacy of provisions made for monitoring and auditing the conduct of the research, including the constitution of a data safety monitoring board (DSMB);

6.2.1.7 the adequacy of the site, including the supporting staff, available facilities, and emergency procedures;

6.2.1.8 the manner in which the results of the research will be reported and published;

6.2.2 Recruitment of Research Participants

6.2.2.1 the characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity);

6.2.2.2 the means by which initial contact and recruitment is to be conducted;

6.2.2.3 the means by which full information is to be conveyed to potential research participants or their representatives;

6.2.2.4 inclusion criteria for research participants;

6.2.2.5 exclusion criteria for research participants;

6.2.3 Care and Protection of Research Participants

6.2.3.1 the suitability of the investigator(s)'s qualifications and experience for the proposed study;

6.2.3.2 any plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action;

6.2.3.3 the medical care to be provided to research participants during and after the course of the research;

6.2.3.4 the adequacy of medical supervision and psycho-social support for the research participants;

6.2.3.5 steps to be taken if research participants voluntarily withdraw during the course of the research;

6.2.3.6 the criteria for extended access to, the emergency use of, and/or the compassionate use of study products;

6.2.3.7 the arrangements, if appropriate, for informing the research participant's general practitioner (family doctor), including procedures for seeking the participant's consent to do so;

6.2.3.8 a description of any plans to make the study product available to the research participants following the research;

6.2.3.9 a description of any financial costs to research participants;

6.2.3.10 the rewards and compensations for research participants (including money, services, and/or gifts);

6.2.3.11 the provisions for compensation/treatment in the case of the injury/disability/death of a research participant attributable to participation in the research;

6.2.3.12 the insurance and indemnity arrangements;

6.2.4 Protection of Research Participant Confidentiality

6.2.4.1 a description of the persons who will have access to personal data of the research participants, including medical records and biological samples;

6.2.4.2 the measures taken to ensure the confidentiality and security of personal information concerning research participants;

6.2.5 Informed Consent Process

6.2.5.1 a full description of the process for obtaining informed consent, including the identification of those responsible for obtaining consent;

6.2.5.2 the adequacy, completeness, and understandability of written and oral information to be given to the research participants, and, when appropriate, their legally acceptable representative(s);

6.2.5.3 clear justification for the intention to include in the research individuals who cannot consent, and a full account of the arrangements for obtaining consent or authorization for the participation of such individuals;

6.2.5.4 assurances that research participants will receive information that becomes available during the course of the research relevant to their participation (including their rights, safety, and well-being);

6.2.5.5 the provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project;

6.2.6 Community Considerations

6.2.6.1 the impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn;

6.2.6.2 the steps taken to consult with the concerned communities during the course of designing the research;

6.2.6.3 the influence of the community on the consent of individuals;

6.2.6.4 proposed community consultation during the course of the research;

6.2.6.5 the extent to which the research contributes to capacity building, such as the enhancement of local healthcare, research, and the ability to respond to public health needs;

6.2.6.6 a description of the availability and affordability of any successful study product to the concerned communities following the research;

6.2.6.7 the manner in which the results of the research will be made available to the research participants and the concerned communities.

6.3 Expedited Review

ECs should establish procedures for the expedited review of research proposals. These procedures should specify the following:

6.3.1 the nature of the applications, amendments, and other considerations that will be eligible for expedited review;

6.3.2 the quorum requirement(s) for expedited review;

6.3.3 the status of decisions (e.g., subject to confirmation by full EC or not).

7 DECISION-MAKING

In making decisions on applications for the ethical review of biomedical research, an EC should take the following into consideration:

7.1 a member should withdraw from the meeting for the decision procedure concerning an application where there arises a conflict of interest; the conflict of interest should be indicated to the chairperson prior to the review of the application and recorded in the minutes;

7.2 a decision may only be taken when sufficient time has been allowed for review and discussion of an application in the absence of non-members (e.g., the investigator, representatives of the sponsor, independent consultants) from the meeting, with the exception of EC staff;

7.3 decisions should only be made at meetings where a quorum (as stipulated in the EC's written operating procedures) is present;

7.4 the documents required for a full review of the application should be complete and the relevant elements mentioned above (see 6.2) should be considered before a decision is made;

7.5 only members who participate in the review should participate in the decision;

7.6 there should be a predefined method for arriving at a decision (e.g., by consensus, by vote); it is recommended that decisions be arrived at through consensus, where possible; when a consensus appears unlikely, it is recommended that the EC vote;

7.7 advice that is non-binding may be appended to the decision;

7.8 in cases of conditional decisions, clear suggestions for revision and the procedure for having the application re-reviewed should be specified;

7.9 a negative decision on an application should be supported by clearly stated reasons.

8 COMMUNICATING A DECISION

A decision should be communicated in writing to the applicant according to EC procedures, preferably within two weeks' time of the meeting at which the decision was made. The communication of the decision should include, but is not limited to, the following:

8.1 the exact title of the research proposal reviewed;

8.2 the clear identification of the protocol of the proposed research or amendment, date and version number (if applicable). on which the decision is based;

8.3 the names and (where possible) specific identification numbers (version numbers/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;

8.4 the name and title of the applicant;

8.5 the name of the site(s);

8.6 the date and place of the decision;

8.7 the name of the EC taking the decision;

8.8 a clear statement of the decision reached;

8.9 any advice by the EC;

8.10 in the case of a conditional decision, any requirements by the EC, including suggestions for revision and the procedure for having the application re-reviewed;

8.11 in the case of a positive decision, a statement of the responsibilities of the applicant; for example, confirmation of the acceptance of any requirements imposed by the EC; submission of progress report(s); the need to notify the EC in cases of protocol amendments (other than amendments involving only logistical or administrative aspects of the study); the need to notify the EC in the case of amendments to the recruitment material, the potential research participant information, or the informed consent form; the need to report serious and unexpected adverse events related to the conduct of the study; the need to report unforeseen circumstances, the termination of the study, or significant decisions by other ECs; the information the EC expects to receive in order to perform ongoing review; the final summary or final report;

8.12 the schedule/plan of ongoing review by the EC;

8.13 in the case of a negative decision, clearly stated reason(s) for the negative decision;

8.14 signature (dated) of the chairperson (or other authorized person) of the EC.

9 FOLLOW-UP

ECs should establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research. The ongoing lines of communication between the EC and the applicant should be clearly specified. The follow-up procedure should take the following into consideration:

9.1 the quorum requirements, the review procedure, and the communication procedure for follow-up reviews, which may vary from the requirements and procedures for the initial decision on an application;

9.2 the follow-up review intervals should be determined by the nature and the events of research projects, though each protocol should undergo a follow-up review at least once a year;

9.3 the following instances or events require the follow-up review of a study:

a. any protocol amendment likely to affect the rights, safety, and/or well-being of the research participants or the conduct of the study;

b. serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies;

c. any event or new information that may affect the benefit/risk ratio of the study;

9.4 a decision of a follow-up review should be issued and communicated to the applicant, indicating a modification, suspension, or termination of the EC's original decision or confirmation that the decision is still valid;

9.5 in the case of the premature suspension/termination of a study, the applicant should notify the EC of the reasons for suspension/termination; a summary of results obtained in a study prematurely suspended/terminated should be communicated to the EC;

9.6 ECs should receive notification from the applicant at the time of the completion of a study;

9.7 ECs should receive a copy of the final summary or final report of a study.

10 DOCUMENTATION AND ARCHIVING

All documentation and communication of an EC should be dated, filed, and archived according to written procedures. A statement is required defining the access and retrieval procedure (including authorized persons) for the various documents, files, and archives.

It is recommended that documents be archived for a minimum period of 3 years following the completion of a study.

Documents that should be filed and archived include, but are not limited to,

10.1 the constitution, written standard operating procedures of the EC, and regular (annual) reports;

10.2 the curriculum vitae of all EC members;

10.3 a record of all income and expenses of the EC, including allowances and reimbursements made to the secretariat and EC members;

10.4 the published guidelines for submission established by the EC;

10.5 the agenda of the EC meetings;

10.6 the minutes of the EC meetings;

10.7 one copy of all materials submitted by an applicant;

10.8 the correspondence by EC members with applicants or concerned parties regarding application, decision, and follow-up;

10.9 a copy of the decision and any advice or requirements sent to an applicant;

10.10 all written documentation received during the follow-up;

10.11 the notification of the completion, premature suspension, or premature termination of a study;

10.12 the final summary or final report of the study.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these Guidelines. The terms may have different meanings in other contexts.

advice

Non-binding considerations adjoined to a decision intended to provide ethical assistance to those involved in the research.

applicant

A qualified researcher undertaking the scientific and ethical responsibility for a research project, either on his/her own behalf or on behalf of an organization/firm, seeking a decision from an ethics committee through formal application.

community

A community is a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and, thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease.

conflict of interest

A conflict of interest arises when a member (or members) of the EC holds interests with respect to specific applications for review that may jeopardize his/her (their) ability to provide a free and independent evaluation of the research focused on the protection of the research participants. Conflicts of interests may arise when an EC member has financial, material, institutional, or social ties to the research.

decision

The response, (either positive, conditional or negative), by an EC to an application following the review in which the position of the EC on the ethical validity of the proposed study is stated.

investigator

A qualified scientist who undertakes scientific and ethical responsibility, either on his/her own behalf or on behalf of an organization/firm, for the ethical and scientific integrity of a research project at a specific site or group of sites. In some instances a coordinating or principal investigator may be appointed as the responsible leader of a team of subinvestigators.

protocol

A document that provides the background, rationale, and objective(s) of a biomedical research project and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.

protocol amendment

A written description of a change to, or formal clarification of, a protocol.

requirements

In the context of decisions, requirements are binding elements that express ethical considerations whose implementation the ethics committee requires or views as obligatory in pursuing the research.

research participant

An individual who participates in a biomedical research project, either as the direct recipient of an intervention (e.g., study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

sponsor

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a research project.

SUPPORTING DOCUMENTS

Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva 1993.

Council for International Organizations of Medical Sciences (CIOMS). *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva 1991.

Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. European Treaty Series – No. 164. Oviedo, 4 April 1997.

Department of Health, Education, and Welfare, Office of the Secretary, Protection of Human Subjects. *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Report of the National Committee for the Protection of Human Subjects of Biomedical and Behavioural Research*. DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014. 18 April 1979.

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) 1 May 1996.

World Health Organization (WHO). Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. Annex 3 of *The Use of Essential Drugs*. Sixth Report of the WHO Expert Committee. Geneva: World Health Organization, 1995: 97-137.

World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical

Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

World Medical Association, *Declaration of Lisbon on the Rights of the Patient*. Adopted by the 34th World Medical Assembly, Lisbon, Portugal, September/October 1981 and amended by the 47th General Assembly, Bali, Indonesia, September 1995.

Operational Guidelines for Ethics Committees Reviewing Biomedical Research

UNDP/World Bank/WHO
Special Programme for Research & Training
in Tropical Diseases
(TDR)

Committees

International Working Party

Solomon Benatar, South Africa

Chifumbe Chintu, Zambia

Francis P. Crawley, Belgium (Chairman)

Dafna Feinholz, Mexico

Christine Grady, USA

Dirceau Greco, Brazil

Hakima Himmich, Morocco

Andrew Kitua, Tanzania

Olga Kubar, Russia

Mary Ann Lansang, Philippines

Reidar Lie, Norway

Vasantha Muthuswamy, India

Renzong Qiu, China

Judit Sándor, Hungary

Secretariat

Juntra Karbwang, TDR WHO (Project Coordinator)

Howard Engers, TDR WHO

David Griffin, WHO

Tikki Pang, WHO

Daniel Wikler, WHO

Myint Htwe, SEARO, WHO

Chen Ken, WPRO, WHO

Abdelhay Mechbal, EMRO, WHO

Antoine Kaboré, AFRO, WHO

Alberto Pellegrini-Filho, AMRO, WHO

Mariam Maluwa, UNAIDS

Claire Pattou, UNAIDS

John Bryant, CIOMS

Ryuichi Ida, UNESCO

Delon Human, WMA

Consultation Partners

Odette Morin Carpentier, International Federation of Pharmaceutical Manufacturers' Associations

Elaine Esber, Food and Drug Administration, USA and FDA Representative to the International Conference on Harmonization

Nadia Tornieporth, SmithKline Beecham Biologics

Wen Kilama, African Malaria Vaccine Testing Network

Robert Eiss, National Institutes of Health, USA

Melody H. Lin, Office for Protection from Research Risks (OPRR), USA

Dixie Snider, Centers for Disease Control and Prevention, USA

Henry Dinsdale, National Council on Ethics in Human Research, Canada

Elaine Gadd, Steering Committee on Bioethics, Council of Europe

Laurence Cordier, European Commission

Fergus Sweeney, European Medicines Evaluation Agency

Betty Dodet, Fondation Marcel Mérieux

Kries De Clerck, European Forum for Good Clinical Practice

Jean-Marc Husson, International Federation of Associations of Pharmaceutical Physicians

Denis Lacombe, European Organization for Research & Treatment of Cancer

Frank Wells, Faculty of Pharmaceutical Medicine, UK

Frédérick Gay, Regional Malaria Control Programme in Cambodia, Laos, and Vietnam, European Commission

BACKGROUND

The *Operational Guidelines for Ethics Committees That Review Biomedical Research* is the result of a wide international consultation begun in August 1999 at A Seminar on the Ethical Review of Clinical Research in Asian & Western Pacific Countries organized by TDR WHO in Chiang Mai, Thailand. The participants at the seminar expressed a need for international guidance on the constitution and operation of ethics committees.

The first draft of these *Guidelines* was discussed at a workshop for members of African Ethical Review Committees organized by TDR WHO and the African Malaria Vaccine Testing Network in Arusha, Tanzania, on 5 November 1999. The draft was subsequently presented to an Interim Meeting of the Forum for Ethical Review Committees in the Asian & Western Pacific Regions (FERCAP) in Bethesda, MD, USA, on 9 November 1999. It was also distributed for consultation at the Global Forum for Bioethics in Research organized by the NIH and WHO in Bethesda on 7-10 November 1999. Following these initial consultations the *Guidelines* were redrafted and widely distributed for comment.

Further development of these *Guidelines* was carried out under the auspices of a Secretariat composed of representatives from WHO, UNAIDS, CIOMS, UNESCO, and the WMA. Responsibility for drafting these *Guidelines* was given to an International Drafting Committee of 14 experts from various continents representing a wide range of disciplines in biomedical research and bioethics. The consultation process was carried out through representatives from the African Malaria Vaccine Testing Network, Council of Europe, European Commission, European Medicines Evaluation Agency, National Institutes of Health (USA), Food & Drug Administration (USA), Office for Protection from Research Risks (USA), Centers for Disease Control and Prevention (USA), National Council on Ethics in Human Research (Canada), Faculty of Pharmaceutical Medicine (United Kingdom), European Organization for Research

& Treatment of Cancer, International Federation of Pharmaceutical Physicians, Foundation Marcel Mérieux, International Federation of Pharmaceutical Manufacturers' Associations, International Conference on Harmonization, and European Forum for Good Clinical Practice. In addition, the draft text was widely distributed to organizations of ethics committees in Europe and the United States as well as to experts in the field of biomedical research ethics. On 2 January 2000 a new draft was prepared and distributed to the members of the Drafting Working Party, the Secretariat, and the Consultation Partners as well as to other parties who had commented or expressed an interest.

Following on the reception of a wide range of detailed comments from around the world, the text was then widely discussed at a Meeting on Guidelines and Standard Operating Procedures for Ethical Review Committees held in Bangkok on 10-12 January 2000. Participants in this meeting were drawn from the regions of Africa, Asia, Latin America, North America, and Europe, from international organizations, (including WHO, UNAIDS, UNESCO, CIOMS, EFGCP, and IFPMA), and from universities and research institutions. A final deliberation took place at a Drafting Meeting held on 13 January 2000 in Bangkok. Following the Drafting Meeting a final set of comments were solicited and integrated into the final document.

The purpose of this wide consultative process was to ensure extensive input while fostering the sharing of knowledge from developing and developed countries alongside organizations and institutions with varying degrees of experience and expertise. This process also help to prepare for the dissemination of the final text through an international process of capacity building that would strengthen national and local infrastructures for ethical review throughout the world.

The *Operational Guidelines for Ethics Committees That Review Biomedical Research* are proposed by the WHO and CIOMS as a support for improving the organization, quality, and standards of

ethical review around the world. These *Guidelines* take into account current practices while suggesting guidance for a harmonized state-of-the-art approach.

Comments and suggestions on all aspects of these guidelines are welcome for consideration in future revisions of this document. Please correspond with:

Dr Juntra Karbwang
Clinical Coordinator
Product Research and Development
TDR/CDS/WHO
CH-1211 Geneva 27
Switzerland

Tel (41) 22 791 3867/8
Fax (41) 22 791 4854
E-mail: karbwangj@who.ch

TDR/PRD/ETHICS/2002.1

Surveying and Evaluating Ethical Review Practices

a complementary guideline to the

Operational Guidelines for Ethics Committees That Review Biomedical Research

Comments and suggestions on all aspects of these guidelines are welcome for consideration in future revisions of this document.

World Health Organization
Geneva
February 2002

TDR/PRD/ETHICS/2002.1

Surveying and Evaluating Ethical Review Practices

a complementary guideline to the

Operational Guidelines for Ethics Committees That Review Biomedical Research

Comments and suggestions on all aspects of these guidelines are welcome for consideration in future revisions of this document

World Health Organization
Geneva
February 2002

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means – electronic, mechanical or other – without the prior written permission of WHO.

The views expressed in documents by named authors, are solely the responsibility of those authors.

© World Health Organization 2002

TABLE OF CONTENTS

PREFACE v

1 OBJECTIVE 1

2 THE ROLE OF AN EC 1

3 THE PURPOSE OF SURVEYING AND EVALUATING ECs 2

4 THE APPROACH TO SURVEYING AND EVALUATING ETHICAL REVIEW 3

5 SOPs FOR SURVEYING AND EVALUATING ETHICAL REVIEW 3

6 ASSIGNING INDEPENDENT SURVEYORS 4

7 CONFLICT OF INTEREST 4

8 CONFIDENTIALITY IN THE SURVEY AND EVALUATION PROCESSES 5

9 WORKING DOCUMENTS 5

10 SURVEY PLAN 5

11 THE CONDUCT OF A SURVEY AND EVALUATION 6

11.1 Opening Meeting 6

11.2 Review of Documentation 7

11.3 Survey Observations 9

11.4 Closing Meeting 10

11.5 The Report 10

11.6 Addressing the Independent Surveyor's Findings and Evaluation 10

11.7 Follow-up 11

11.8 Final Report 11

GLOSSARY 13

SUPPORTING DOCUMENTS 17

SURVEYING AND EVALUATING ETHICAL REVIEW PRACTICES 19

PREFACE

In 2000 TDR WHO introduced the *Operational Guidelines for Ethics Committees That Review Biomedical Research*, which has contributed globally to the development of independent and competent ethical review. The *Operational Guidelines* provide essential guidance for the development of the constitution, composition, and procedures of ethics committees (ECs) and ethical review systems. The ethical review of research involving human participants provides an essential measure for safeguarding and promoting the protection of persons and communities.

This guideline on *Surveying and Evaluating Ethical Review Practices* is intended to be complementary to the *Operational Guidelines*. Its purpose is to facilitate and support procedures for assisting the development of quality and transparency in ethical review. The Guideline is developed as a means to contribute to the education of ethics committees through review and evaluation of their practices. It is also intended to contribute to justified public confidence in the ethical review of research involving human participants. Finally, this Guideline is intended to assist public authorities and national associations involved with developing ethical review systems in promoting good ethical review practices.

The ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the WHO & ICH Guidelines for Good Clinical Practice. Adherence to guidelines, as well as national legislation and other instruments, helps to ensure that the dignity, rights, safety, and well being of research participants are promoted and that the results of the investigations are credible.

This Guideline relies on the established standards for international research ethics and Good Clinical Practice as the primary reference for surveying and evaluating the practices of ECs. In particular, the WHO

& ICH Good Clinical Practice Guidelines provide a fundamental framework for appreciating the role and responsibilities of ECs in the research process. The specific needs for the composition and functioning of an EC are provided in the TDR WHO *Operational Guidelines for Ethics Committees That Review Biomedical Research.* The *Declaration of Helsinki* provides a general ethical framework for all persons engaged in the conduct of biomedical research.

1 OBJECTIVE

The purpose of this Guideline is to contribute to an international framework for surveying and evaluating ethical review practices. Ethical review provides essential guidance on research proposals and helps to ensure the protection of participants. The assurance of research protections for individuals and communities requires the establishment of standards for ethical review and the evaluation of the performance of ethical review systems, including the functioning of ECs.

More recently there is growing national and international interest in ensuring that ethical review achieves the highest standards with regard to the protection of individuals and communities. Some countries and regions are in the process of determining methods for evaluating the performance and quality of ECs. In particular, accreditation systems for ECs based on an evaluation of their constitution, Standard Operating Procedures (SOPs), and practices are under development in several countries. This Guideline provides a common reference point for appreciating good ethical review practices and promoting transparency in the work of ECs.

ECs have a public responsibility whose fulfilment requires good practices for ethical review as well as the ongoing education of their members. As part of good practices, there should be a system of quality assurance for surveying and evaluating the performance of ethical review systems. This involves the development by ECs of internal quality assurance mechanisms, such as self-assessment checklists, designed for self-appraisal. Further measures include independent external evaluations of EC practices designed to advise, educate, and improve the ethical review process.

2 THE ROLE OF AN EC

ECs have been established to provide ethical advice to researchers in order to assist decision-making on the adequacy of proposed research projects regarding the protection of potential and actual human partici-

pants. In order to fulfil this role it is essential that ECs are constituted and perform according to four principles for ethical review: independence, competence, pluralism, and transparency.

The *Declaration of Helsinki*, Good Clinical Practice Guidelines, and other international and national instruments require the ethical review of research prior to its commencement. These instruments also require ECs to perform regular follow-ups to research projects for which they have provided a positive decision. In their decision-making, ECs must be independent of the sponsor, the investigator, and any undue influence.

ECs must be appropriately constituted and adopt written SOPs in order to achieve independence and quality in decision-making.

3 THE PURPOSE OF SURVEYING AND EVALUATING ECs

The purpose of surveying and evaluating ethical review practices is to assist ECs in reviewing their practices and appraising performance while also providing a means to assure the public that the ethical review of research proposals is carried out according to established standards. The survey should establish the basis for an independent evaluation that provides relevant information to parties having a legitimate interest in the appropriate functioning of an EC, as defined within the framework of national legislation or mutually agreed to by the surveying entity and the EC. An independent evaluation should provide an opportunity for an EC to receive advice on its constitution and operation.

In recent years ECs along with health ministries and regulatory authorities have taken measures to improve the process of ethical review. In some instances these measures have included independent reviews and evaluations of ECs as a means to improve practices and achieve more confident results. There has also been an interest on the part of researchers and sponsors to have more information regarding the functioning of ECs.

At present only a few countries have a legal or regulatory framework for assisting in the evaluation of ECs, while the framework for the inspection of clinical trials is well established in some countries. This Guideline suggests a cooperative and educative model for surveying and evaluating the work of ECs, being concerned less with 'enforcement' of standards and more with 'learning' from the review of practices.

4 THE APPROACH TO SURVEYING AND EVALUATING ETHICAL REVIEW

A predefined framework should be established for surveying and evaluating ethical review practices. Such a framework may be established by national health or regulatory authorities, or it may be agreed upon in cooperation with national, regional, or international associations. The framework should define the responsible entities for surveying and evaluating ECs as well as the circumstances and frequency of the reviews. Where no predefined framework exists, ECs should be able to avail themselves of surveillance and/or evaluative processes or other quality assurance mechanisms.

Open and frank communication should characterise the surveying and evaluative procedures, with both the independent surveyor and the EC providing a supportive structure. Independent surveyors should be bound by a confidentiality agreement prior to the commencement of the review procedures.

5 SOPs FOR SURVEYING AND EVALUATING ETHICAL REVIEW

SOPs for surveying and evaluating ethical review practices should be developed in advance of the activities taking place. These SOPs should provide detailed guidance on the requirements for assigning independent surveyors, as well as procedures related to conflict of interest and confidentiality, the development of survey plans, the documents to be reviewed, and the writing of the evaluative report and its distribution. The SOPs should be based on the predefined framework for surveying

and evaluating ethical review systems and/or the actual practices of specific ECs. These SOPs should be flexible, where necessary, in order to meet the needs of specific systems and their ECs while permitting comprehensives reviews.

6 ASSIGNING INDEPENDENT SURVEYORS

Independent surveyors should be appropriately trained and qualified for carrying out the review of ethical review practices. The assignment of an independent surveyor or surveying entity should be based on qualifications expressed in SOPs for a regional, national, local, or specific ethical review system.

Independent surveyors should have experience in working with quality evaluation, preferably within ethical review systems. They should also have demonstrated communication skills and preferably experience in education. Independent surveyors should be thoroughly familiar with the requirements, practices, and needs of ECs, and they should be knowledgeable of the legislative and regulatory framework in which the EC to be reviewed is working.

7 CONFLICT OF INTEREST

The independence of the surveyor is an essential guarantee for the validity of the survey and evaluation findings. Any real or potential conflict of interest on the part of an (candidate) independent surveyor should be declared prior to the review activity to both the entity responsible for assigning the independent surveyor and the EC. A conflict of interest on the part of an independent surveyor may include financial, research, and/or professional involvement on the part of the independent surveyor with institutions or persons submitting applications to the EC or direct involvement of the independent surveyor with the EC. Where substantial conflict of interest is determined, the assignment of the independent surveyor should not take place or be withdrawn.

8 CONFIDENTIALITY IN THE SURVEY AND EVALUATION PROCESSES

The survey and evaluation processes should be designed to guarantee the full confidentiality of patients/research participants, community, and research design and data. The independent surveyor should sign a confidentiality agreement prior to the initiation of any survey-related activities that bars the disclosure of information considered confidential to patients/research participants, communities, researchers, sponsors, or the EC itself. Correspondence and information related to the survey and evaluation processes, including the final report, should not contain confidential information. In addition, the findings as well as the final report should be available only to those parties defined in advance by the entity responsible for conducting the survey and evaluation or otherwise mutually agreed to by the independent surveyor and the EC.

9 WORKING DOCUMENTS

An independent surveyor should review the standards, regulations, guidelines, constitution, SOPs, and/or project specific requirements applicable to an EC. In addition, the working documents of an EC may be reviewed, including meeting minutes and official correspondence.

10 SURVEY PLAN

A survey plan should be designed for each review activity, taking into consideration the reason for the review. The survey plan should be drafted by the independent surveyor and communicated in advance to the EC for agreement. The plan should be designed in accordance with an SOP for surveying and evaluating ethical review practices.

The survey plan should include the following:

10.1 identification and location of the independent surveyor;

10.2 identification and location of the EC, as well as the persons responsible for representing the EC during the survey and evaluation;

10.3 identification of the persons to be interviewed by the independent surveyor;

10.4 reason for the survey and evaluation;

10.5 objectives and scope of the survey and evaluation;

10.6 expected time and duration for each major survey and evaluation activity;

10.7 date(s) and location of the survey and evaluation;

10.8 schedule and purpose of meeting(s) to be held between the independent surveyor and the EC;

10.9 language in which the survey and evaluation is to be conducted and any arrangements for translation;

10.10 confidentiality requirements and confidentiality statements;

10.11 identification of reference documents to be used by the independent surveyor (for example, the applicable standards, regulations, guidelines, SOPs);

10.12 documents of the EC to be reviewed (for example, constitution, SOPs, minutes of meetings, relevant correspondence);

10.13 distribution of the report, if applicable;

10.14 foreseen follow-up actions to the survey and evaluation;

10.15 expected date of the survey and evaluation completion.

11 THE CONDUCT OF A SURVEY AND EVALUATION

The survey and evaluation of an EC should be conducted according to a mutually agreed survey plan that includes the following:

11.1 Opening Meeting

The survey and evaluation begins with an opening meeting between the independent surveyor and the representative(s) of the EC. These representatives should be appointed in accordance with the SOPs of the EC or determined by the chairperson of the EC. It is expected that an

officer (for example, chairperson, assistant chairperson, or secretary) will be present at the opening meeting.

The objectives of the Opening Meeting include the following:

11.1.1 review of the purpose and scope of the survey and evaluation;

11.1.2 review of the survey plan;

11.1.3 discussion of the documents to be reviewed;

11.1.4 discussion of the current practices of the EC;

11.1.5 discussion of any considerations relating to laws, regulatory requirements, or guidelines affecting EC practices;

11.1.6 clarification of arrangements for contacting the representatives of the EC during the survey and evaluation;

11.1.7 confirmation of the time and date for the closing meeting.

11.2 Review of Documentation

The independent surveyor is required to review the constitution and SOPs of an EC. The independent surveyor may also need to consider other working documents of an EC, such as the application form, decision form, specific procedures for reviewing certain kinds of protocols, evaluation forms for reviewing applications, and minutes of meetings. The documents to be reviewed may include the following information:

11.2.1 Documents Referring to the Establishment of the EC

11.2.1.1 the authority under which the EC was established;

11.2.1.2 a statement from the EC indicating the relevant laws, regulatory requirements, as well as appropriate national and international guidelines according to which it operates;

11.2.2 Documents Referring to the Membership of the EC

11.2.2.1 the membership requirements;

11.2.2.2 the terms and procedure for the appointment of members of the EC;

11.2.2.3 the conditions of appointment;

11.2.2.4 a listing of current and previous members of the EC;

11.2.2.5 the curriculum vitae of current and past members of the EC;

11.2.2.6 a description of the requirements for holding EC offices (for example, chairperson, secretary);

11.2.2.7 a description of the responsibilities and duties of the offices of the EC;

11.2.2.8 the quorum requirements;

11.2.3 Documents Referring to Applications Made to the EC

11.2.3.1 the published guidelines for submission of applications for the review by the EC;

11.2.3.2 the required documentation to be included in the application;

11.2.3.3 the registration procedure for applications;

11.2.3.4 the maintenance of records for communications regarding the application;

11.2.3.5 the review procedure timelines;

11.2.4 Documents Referring to Review Procedures of the EC

11.2.4.1 the meeting procedures;

11.2.4.2 the provisions and conditions for expedited EC review and decision;

11.2.4.3 the elements of the review of the application;

11.2.4.4 the decision-making procedure;

11.2.4.5 the procedure for communicating a decision;

11.2.4.6 the follow-up review;

11.2.4.7 the documentation and archiving procedures;

11.2.5 Documents Referring to Actions Taken by the EC

11.2.5.1 the materials submitted by applicants;

11.2.5.2 the correspondence regarding applications, decisions, and follow-ups;

11.2.5.3 the record of incomes and expenses of the EC;

11.2.5.4 the agenda of EC meetings;

11.2.5.5 the minutes of EC meetings;

11.2.5.6 the decisions and advice provided to applicants;

11.2.5.7 interim and annual reports during follow-up;

11.2.5.8 notifications of completion or premature study suspensions/ terminations;

11.2.5.9 final summaries or reports of studies;

11.2.5.10 regular (annual) reports of the EC.

The independent surveyor should also review the manner in which documents are filed and stored, including previous versions of the EC constitution and/or SOPs.

11.3 Survey Observations

All survey findings should be documented. Following the survey, the independent surveyor should review the findings and present an evaluation. The independent surveyor should ensure that these findings are documented in a clear and concise manner, without disclosing any patient/participant, researcher, sponsor, and EC information of a confidential nature. The findings should be, where possible, supported by objective evidence and reference made to the relevant requirements. The evaluation based on the findings should assist the EC in improving its working procedures.

11.4 Closing Meeting

At the conclusion of the survey and evaluation, a meeting should be held with the independent surveyor and EC to review the findings and clarify any misunderstandings. The meeting should be of a mutually supportive nature.

11.5 The Report

The report should reflect the findings and evaluation of the independent surveyor. It should be dated and signed by the independent surveyor and contain, at the minimum, the following items:

11.5.1 identification of the independent surveyor;

11.5.2 identification of the EC and the representative(s) of the EC;

11.5.3 objectives and scope of the survey and evaluation;

11.5.4 survey plan;

11.5.5 identification of the facilities, persons interviewed, and the documents reviewed;

11.5.6 findings of the survey;

11.5.7 the independent surveyor's evaluation based on the findings;

11.5.8 observations and recommendations for corrective actions or areas of suggested revisions in practice;

11.5.9 report distribution list;

11.5.10 signature and date of the independent surveyor.

Both the independent surveyor and the EC should retain a copy of the report for the same time period for which the EC stores essential records.

11.6 Addressing the Independent Surveyor's Findings and Evaluation

The EC is responsible for determining, initiating, and completing the actions required to address the findings and evaluation as presented in the report. These actions and a time period for their accomplishment

should, if appropriate, be communicated to the independent surveyor within a reasonable time period following the receipt of the report.

11.7 Follow-up

A follow-up survey and evaluation may be appropriate. A survey plan should be prepared by the independent surveyor for the follow-up review and agreed to by the EC. The EC is responsible for determining, initiating, and completing the actions required to address the findings and evaluation as presented in the follow-up report.

11.8 Final Report

The independent surveyor should present a final report containing the final set of findings and an overall evaluation supported, where possible, by objective evidence. The final report should be communicated to the entity under which the survey and evaluation takes place, the EC, and others as defined within the framework of national law or as mutually agreed by the surveying entity and the EC.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these Guidelines. The terms may have different meanings in other contexts.

Community

A community is a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease.

Confidentiality Agreement

An agreement signed by the independent surveyor prior to the initiation of a survey or any survey-related activities that bars the independent surveyor, the survey and evaluation process, and the report from the disclosure of any patient/participant, researcher, sponsor, and EC information of a confidential nature.

Conflict of Interest

A conflict of interest arises when an independent surveyor holds any real or potential financial, research, and/or professional interests that may affect the validity of the survey findings and evaluation.

Constitution

A document establishing the authority under which an EC is established, the mandate and remit of an EC, and general provisions for its activities. The term 'constitution' may be replaced at times by other terms, such as 'terms of reference'.

Decision

The response (positive, conditional, or negative) by an EC to an applicant following the review of an application.

Evaluation

The assessment by an independent surveyor of the strong and weak points of an EC's practices based on the findings of a survey.

Findings

The findings of a survey based on the purpose of the survey and the materials reviewed by the independent surveyor. The findings should refer to specific observations made by the independent surveyor and be supported by objective evidence. Findings express the independent surveyor's conclusions regarding specific procedures or systems reviewed according to the relevant requirements. The findings are the basis for the independent surveyor's evaluation of the ethical review practices of an EC.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of research participants are protected.

Independent Surveyor

The person(s) responsible for carrying out the survey and evaluation of an EC.

Report

A written evaluation by the independent surveyor of the results of the survey and evaluation. The report may take the form of an 'initial report', 'follow-up report', or 'final report'. In all cases the report should not

disclose any patient/participant, researcher, sponsor, and/or EC information of a confidential nature.

Research Participant

An individual who participates in a research project, either as the direct recipient of an intervention (for example, study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

Sponsor

An individual, company, institution, or organisation that takes responsibility for the initiation, management, and / or financing of a research project.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity in the performance of a specific function.

Survey

The activity of reviewing ethical review practices, usually those of a specific EC, in order to analyse and evaluate those practices with a view toward quality improvement and transparency.

Survey Plan

A plan setting out the specific practices, resources, activities, and timelines relevant to a particular survey and evaluation.

SUPPORTING DOCUMENTS

Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva 1993.

Council for International Organizations of Medical Sciences (CIOMS). *International Guidelines for Ethical Review of Epidemiological Studies.* Geneva 1991.

Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.* European Treaty Series – No. 164. Oviedo, 4 April 1997.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal* L121 34-44, 1 May 2001.

European Forum for Good Clinical Practice. *European Guidelines for Auditing Independent Ethics Committees.* Brussels: The EFGCP News, Summer 2001.

European Forum for Good Clinical Practice. *Guidelines and Recommendations for European Ethics Committees.* Revised Edition. Brussels: EFGCP, 1997.

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) 1 May 1996.

World Health Organization (WHO). *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products.* Annex 3 of *The Use of Essential Drugs.* Sixth Report of the WHO Expert Committee. Geneva: World Health Organization, 1995: 97-137.

World Health Organization (TDR/WHO). *Operational Guidelines for Ethics Committees That Review Biomedical Research*. Geneva: WHO, 2000.

World Medical Association, *Declaration of Helsinki: Ethical Principles for Research Involving Human Subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; the 48th General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd General Assembly, Edinburgh, Scotland, October 2000.

Surveying and Evaluating Ethical Review Practices

a complementary guideline to the

Operational Guidelines for Ethics Committees That Review Biomedical Research

This guideline was prepared following broad international consultation, including presentation and discussion at international meetings held in Manila, The Philippines; Pretoria, South Africa; Buenos Aires, Argentina; Berlin, Germany; Geneva, Switzerland; and Bethesda, Maryland, USA.

International Research and Drafting Committee

Francis P. Crawley (Chairman)
European Forum for Good Clinical Practice

Odette Morin Carpentier
International Federation of Pharmaceutical Manufacturer's Association

Chifumbe Chintu
Pan-African Bioethics Initiative

Vichai Chokevivat
Forum for Ethical Review Committees in Asia & Western Pacific

Christiane Druml
Ethical Review Committee, Vienna University School of Medicine, Austria

Elaine Esber
Merck Sharp & Dohme

Dafna Feinholz
Foro Latino Americano de Comités de Ética en Investigacion en Salud [Latin American Forum of Ethics Committees in Health Research] (FLACEIS)

Victoria Hale
Institute for One World Health, USA

Kenji Hirayama
Saitama Medical School, Japan

Greg Koski
Office for Human Research Protections
Department of Health and Human Services, USA

Olga Kubar
Forum for Ethics Committees in the Confederation of Independent States

James Lavery
National Institutes of Health, USA

David Lepay
Food and Drug Administration, USA

Melody Lin
Office for Human Research Protections
US Department of Health and Human Services, USA

Marianne Maman
Novartis Pharmaceuticals

Vasantha Muthuswamy
Indian Council of Medical Research

Sara Radcliffe
Pharmaceutical Research & Manufacturers Association of America

John Richardson
Central Office for Research Ethics Committees, United Kingdom

John Sweatman
European Forum for Good Clinical Practice

Fergus Sweeney
European Agency for the Evaluation of Medicinal Products

Nadia Tornieporth
GlaxoSmithKline Pharmaceuticals

Peteris Zilgalvis
Council of Europe

Secretariat

Juntra Karbwang (Project Coordinator)
TDR/WHO

Howard Engers
TDR/WHO

Christine Encrenaz
Essential Drugs & Other Medicines, WHO

Chen Ken
WPRO/WHO

Adik Wibowo
SEARO/WHO

Comments and suggestions on all aspects of these guidelines are welcome for consideration in future revisions of this document. Please correspond with:

Dr Juntra Karbwang
Clinical Coordinator
Product Research and Development
TDR/CDS/WHO
CH-1211 Geneva 27
Switzerland

Tel (41) 22 791 3867/8
Fax (41) 22 791 4854
E-mail: karbwangj@who.ch

TDR/GEN/Guidelines/05.1

0

Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards

UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

TDR/GEN/Guidelines/05.1

Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards

UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

Copyright © World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases 2005

All rights reserved.

The use of content from this health information product for all non-commercial education, training and information purposes is encouraged, including translation, quotation and reproduction, in any medium, but the content must not be changed and full acknowledgement of the source must be clearly stated. A copy of any resulting product with such content should be sent to *TDR, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland.* TDR is a World Health Organization (WHO) executed UNICEF/UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases.

This information product is not for sale. The use of any information or content whatsoever from it for publicity or advertising, or for any commercial or income-generating purpose, is strictly prohibited. No elements of this information product, in part or in whole, may be used to promote any specific individual, entity or product, in any manner whatsoever.

The designations employed and the presentation of material in this health information product, including maps and other illustrative materials, do not imply the expression of any opinion whatsoever on the part of WHO, including TDR, the authors or any parties cooperating in the production, concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delineation of frontiers and borders.

Mention or depiction of any specific product or commercial enterprise does not imply endorsement or recommendation by WHO, including TDR, the authors or any parties cooperating in the production, in preference to others of a similar nature not mentioned or depicted.

WHO, including TDR, and the authors of this health information product make no warranties or representations regarding the content, presentation, appearance, completeness or accuracy in any medium and shall not be held liable for any damages whatsoever as a result of its use or application. WHO, including TDR, reserves the right to make updates and changes without notice and accepts no liability for any errors or omissions in this regard. Any alteration to the original content brought about by display or access through different media is not the responsibility of WHO, including TDR, or the authors.

WHO, including TDR, and the authors accept no responsibility whatsoever for any inaccurate advice or information that is provided by sources reached via linkages or references to this health information product.

TABLE OF CONTENTS

INTRODUCTION 1

1 OBJECTIVE 3

2 THE NEED FOR A DSMB 3

3 THE PLACE OF A DSMB 5

4 THE ROLE OF A DSMB 5

5 CONSTITUTING A DSMB 6

6 CHARTER AND OPERATIONS OF A DSMB 7

6.1 DSMB Charter 7

6.1.1 Description 8

6.1.2 Objectives 9

6.1.3 Meeting arrangements 9

6.1.4 Data management and security 9

6.1.5 Documentation 10

6.2 Operations of a DSMB 10

6.2.1 Membership 10

6.2.2 Terms of appointment 11

6.2.3 Conditions of appointment 11

6.2.4 Offices 12

6.2.5 Independant Consultants 12

6.2.6 Conflict of Interest 13

6.2.7 Education for DSMB Members 13

6.2.8 Staff 13

6.2.9 Quorum Requirements 13

6.2.10 Meeting Requirements 14

6.2.11 Meeting Procedures 14
6.2.12 Format of Meetings 17
6.2.13 DSMB Review of the Sponsor Report 17
6.2.14 Arriving at Recommendations 18
6.2.15 Minutes of the DSMB Meeting 19
6.2.16 Communicating the DSMB Recommendations .. 20
6.2.17 DSMB Recommendation Distribution 21
6.2.18 Documentation and Archiving 21
GLOSSARY 23
SUPPORTING DOCUMENTS 27
7 COMMITTEES 31
International Working Parties 31
Consultation Partners 32
Secretariat 34
8 BACKGROUND 35

INTRODUCTION

These Operational Guidelines are intended to provide international guidance to health research sponsors for the establishment and functioning of data and safety monitoring boards (DSMBs). The guidelines are based on a review of the existing guidances and requirements for DSMBs from national and international organizations, as well as on observation of existing practices of DSMBs in countries and institutions around the world.

Ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the Council of International Organizations of Medical Sciences (CIOMS) International ethical guidelines for biomedical research involving human subjects, and the WHO and ICH Guidelines for good clinical practice. The WHO/TDR Operational guidelines for ethics committees that review biomedical research have contributed to the development of ethical review practices in health research, establishing an international standard for promoting quality and consistency in ethical review. Compliance with international ethical and scientific guidance in health research contributes to ensuring that the dignity, rights, safety, and well-being of research participants are promoted and that the results of investigations are valid.

For more than 50 years, the randomized controlled clinical trial has been recognized as the standard method for evaluating the safety and efficacy of a medical intervention. The process of comparing alternative treatments and arriving at conclusive results is rigorous and complex. An essential ethical consideration in research involving human subjects is that studies should not be continued if the design of the study is no longer appropriate. Studies may also require early termination if there is strong evidence that the study has already achieved its primary objectives, the accrued evidence indicates the primary objective(s) will likely not be achieved, or there is a negative trend in the benefit/risk(harm) ratio. Furthermore, a study may need to be modified if it is observed that the accrued

data are not in line with the study design assumptions. These considerations may be especially appropriate for studies with serious outcomes or endpoints, such as mortality, serious morbidity, or irreversible adverse effects.

To preserve the integrity of the study and/or to protect the rights and welfare of research participants, there may be a need for the DSMB to recommend, at certain points, modifications to the study. These recommendations generally relate to patient safety and may include recommendations concerning dosages, treatment duration, and/or concomitant therapy. DSMBs may also include recommendations regarding eligibility criteria, sample size, and/or participant recruitment rate. Under these circumstances, sponsors and investigators may need independent advice for making such decisions. In order to ensure scientific integrity of the study, protection of human subjects, credibility of data, and avoidance of conflict of interest, an independent DSMB may be essential, especially for complex or pivotal studies. It is now recognized that a DSMB is often in the best position to provide independent assessment of the continued appropriateness and safety of an ongoing study, so the highest possible scientific and ethical standards are adhered to and maintained in the study.

1 OBJECTIVE

The objective of these Guidelines is to contribute to the preservation of scientific integrity and protection of human subjects in health research. These Guidelines describe the constitution, role, responsibilities, and operating framework for DSMBs. The Guidelines are intended to complement existing regulations and practices, as well as serve as a basis upon which specific written procedures for the functions of a DSMB can be developed by the sponsor. In this regard, the Guidelines provide international guidance to assist sponsors in developing, evaluating, and progressively refining DSMB charters and operating procedures. They are also intended to assist DSMB members, sponsors, investigators, members of ethics committees, regulatory authorities, and research participants and their organizations in understanding the role and functions of DSMBs. Users of the Guidelines should be mindful of their local laws and regulations as they apply to health research, especially as they concern the establishment and operations of DSMBs. The Guidelines are not intended to supersede national laws and regulations.

2 THE NEED FOR A DSMB

All clinical studies require safety monitoring throughout the duration of the research, but not all studies require monitoring by a DSMB. DSMBs may be critical for studies intended to save lives, prevent serious disease progression, or reduce the risk of a major adverse health outcome. DSMBs are particularly important in studies where interim data analysis is required to ensure the safety of research participants. A DSMB is often considered relevant in the following kinds of studies:

2.1 Controlled studies with mortality and/or severe morbidity as a primary or secondary end-point.

2.2 Randomized controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality.

2.3 Early studies of a high-risk intervention (risk of non-preventable, potentially life-threatening, complications; or risk of common, preventable adverse events of interest [especially type A drug reactions]), whether or not randomized.

2.4 Studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes.

2.5 Studies where the design or expected data accrual is complex, or where there may be ongoing questions with regard to the impact of accrued data on the study design and participants' safety, particularly in studies with a long duration.

2.6 Studies where the data justify its early termination, such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality.

2.7 Studies carried out in emergency situations.

2.8 Studies which involve vulnerable populations.

Not all studies within the above categories require DSMBs. Conversely, there may be other sound reasons for establishing DSMBs for certain studies that fall outside the above categories. In general, sponsors should consider the need for establishing a DSMB prior to undertaking a particular study. An ethics committee may also suggest to the sponsor that a DSMB be established for a particular study.

Although the DSMB has no direct relationship with the ethics committee, all protocol revisions approved by the ethics committee should be submitted to the DSMB. Other site-specific amendments may require special treatment.

3 THE PLACE OF A DSMB

The DSMB occupies a unique and important place in studies requiring specialized monitoring for data and safety. Constituted and functioning under the authority of the sponsor, a DSMB is an independent advisory body responsible for assessing data during the course of a study in a manner that contributes to the scientific and ethical integrity of the study.

The DSMB's recommendations provide the sponsor with an overall scientific, safety, and ethical appreciation of the study, and should assist the sponsor in maintaining the rigour of the study design, with appropriate attention paid to the protection of human subjects.

Safety monitoring should be part of all clinical trials, but responsibility for this may never be solely that of a DSMB. Serious adverse events (SAEs) should be regularly monitored by sponsors and reported to the appropriate parties according to regulatory requirements. In addition, safety data (often still blinded) should be monitored by the study investigators and data managers.

It is essential that all parties (including research participants, investigators, sponsors, ethics committees, regulatory authorities, and other study personnel) who are engaged in a study have confidence in the function and decisions of the DSMB. While the recommendations of a DSMB are communicated directly to the sponsor, the sponsor should notify other relevant parties and ensure that the recommendations are communicated to, and acted upon by, the various parties involved during the course of the study.

4 THE ROLE OF A DSMB

At intervals defined by the protocol, the DSMB reviews and evaluates the data on clinical efficacy and safety collected during the study, and assesses reports on cumulated serious adverse events (SAEs). The DSMB may also be requested by the sponsor to conduct emergency reviews of data to assess safety-related issues. While not responsible for the quality of data, the DSMB may be asked to

monitor this aspect. At the conclusion of the review, the DSMB provides a written recommendation to the sponsor regarding whether a protocol should be amended and/or a study should proceed based on its review of the data and the progress report submitted by the sponsor.

A DSMB should provide independent, competent, and timely review of the data from an ongoing study. The composition, review, and decision-making procedures of this Board should be free from political, social, institutional, professional, and market influences. The Board's procedures should promote independence in decision-making vis-à-vis the sponsor; at the same time, the DSMB needs to demonstrate competency and efficiency in its work.

For many trials, sequential review of safety and efficacy data may be used to permit early termination in the event of extremely strong results. Such sequential designs are primarily appropriate for studies with a major outcome, e.g. death, stroke, or irreversible progression of serious disease. A DSMB may recommend that the sponsor suspends or terminates a study whenever it is deemed necessary for safety reasons.

5 CONSTITUTING A DSMB

When required by the nature of a study, a sponsor should establish a DSMB to ensure the broadest possible coverage of potential research participants, and the validity and scientific integrity of the data. The sponsor is responsible for establishing the DSMB's charter, which should be included (or referred to) in the study protocol. This may be undertaken with advice from investigators or other parties involved in the study.

The sponsor is responsible for constituting a DSMB in such a way that review and evaluation of accumulated data during the course of the study can be executed competently and free from bias or influence that could affect the independence of the DSMB decision-making. The amount of payments and/or compensations made to DSMB members should be reasonable so as not to constitute coercion.

The sponsor is responsible for the selection and appointment of DSMB members as well as for ensuring that the DSMB has the means and resources to function well. In order to generate competent reviews and sound recommendations, the DSMB should be multi-disciplinary and include, as appropriate, expertise in medicine (physicians with relevant backgrounds), clinical pharmacology and/or toxicology, epidemiology, statistics, clinical trial process, and ethics. The suitability of members of a board should be determined according to the nature of the study to be monitored. Appropriately qualified members who are able to act independently are essential to the DSMB's role in ensuring integrity of the research and safety of the patients/participants. The DSMB should be fully constituted and should meet to review its charter and the study protocol before the study begins.

In international studies, representation should be considered from participating countries. For studies conducted in settings with limited healthcare research infrastructure, it may be appropriate to have additional types of expertise represented on the DSMB. For example, anthropologists or community members may be of value in assessing cultural sensitivities that may affect interpretation of data. To this end, it may also be advantageous for large, international multicentre studies to have representation on the DSMB from more than one country.

6 CHARTER AND OPERATIONS OF A DSMB

6.1 DSMB Charter

The sponsor should establish a DSMB charter that defines the relationship between the sponsor and the DSMB. The charter should be developed according to the data monitoring needs (including scientific and ethical) of the particular study. The charter should identify the study for which the DSMB is established and the role and responsibilities of the DSMB in the study.

The charter should indicate the authority under which the DSMB is constituted together with its responsibility, operational procedures, means of communications, and decision-making procedures - when and as applicable - vis-à-vis the sponsor, the investigator(s), study statistician, data manager, ethics committee(s), and regulatory authority(ies).

The relationship between the DSMB and other parties with responsibilities in the study should be clearly defined in order to avoid conflict in decision-making arising during the course of the study. The role and responsibilities of the DSMB should be clearly identified vis-à-vis those of the investigator(s) and ethics committee(s). Equally important is establishing the role and responsibilities of the DSMB in reference to the study steering committee, statisticians, data managers, clinical research associates, auditors, and other relevant offices of the sponsor.

At times a single DSMB may be established for a set or programme of studies, or for multiple studies. In this case, the charter should reflect the consistencies and specificities of the DSMB's responsibilities and activities across the studies.

The following items should be addressed in the charter. Some of the items identified may be addressed within the charter; others may be addressed in separate standard operating procedures (SOPs). The decision as to which procedures should be included in the charter and which ones in separate SOPs will be specific to the study.

6.1.1 Description

6.1.1.1 The name or description of the individual or office of the sponsor responsible for appointing members to the DSMB.

6.1.1.2 An organizational diagram indicating the relationship of the DSMB to other parties in the study: the sponsor (including the steering committee and Contract Research Organization), investigator, and ethics committee.

6.1.1.3 A description of the membership requirements of the DSMB (including qualifications, payments and/or compensations).

6.1.1.4 Arrangements for audits and/or inspections of the DSMB.

6.1.2 Objectives

6.1.2.1 Data that are to be reviewed by the DSMB.

6.1.2.2 Intervals (specific times) at which the DSMB will review and evaluate the data.

6.1.2.3 Points to be evaluated and advised on by the DSMB.

6.1.2.4 Statistical procedures to be utilized by the DSMB (including procedures for monitoring safety and efficacy outcomes, and/or ongoing benefit/risk[harm] analysis, as appropriate).

6.1.2.5 Parties to whom the DSMB report will be distributed by the sponsor (e.g. investigator(s), ethics committee(s), regulatory authority(ies), the study steering committee, data managers).

6.1.3 Meeting arrangements

6.1.3.1 Materials to be forwarded to the DSMB members and meetings.

6.1.3.2 Process and format of the DSMB meetings.

6.1.3.3 Quorum requirements.

6.1.3.4 Procedures for maintaining study confidentiality.

6.1.4 Data management and security

6.1.4.1 Where and how the data examined by the DSMB will be stored and maintained.

6.1.4.2 Who will have access to the data.

6.1.4.3 How the confidentiality and privacy of the data will be maintained.

6.1.4.4 How personally identifiable data will be handled.

6.1.5 Documentation

6.1.5.1 The confidentiality agreement(s) signed by DSMB members.

6.1.5.2 The format and content of the minutes of DSMB meetings.

6.1.5.3 The format and content of DSMB reports.

6.1.5.4 The procedure for amending the DSMB charter.

6.1.5.5 The procedure for record-keeping and archiving.

After reviewing the charter, all DSMB members should agree to, and sign, the charter at the time of their appointment to the DSMB. The members' signatures' indicate their intent to fulfil their DSMB responsibilities.

6.2 Operations of a DSMB

The responsibilities of the DSMB as outlined in the charter should be fulfilled according to the requirements of the study. The sponsor should develop its standard operating procedures (SOPs) in accordance with the needs of the charter. The SOPs may be procedures that apply to all DSMBs established by a sponsor, adapted as appropriate to the charter and needs of the particular DSMB.

6.2.1 Membership

The DSMB is an independent multidisciplinary group consisting of at least three members. It should include individuals with relevant clinical and statistical expertise. Additional expertise may be required in certain studies, e.g. in the specific disease area being studied, or in ethics. The size and necessary expertise of the DSMB will depend upon the study design. Members should not be affiliated

with the sponsor, investigator(s), ethics committee(s), regulatory authority(ies), site(s) or study staff. Members should also not have vested conflicts of interest (e.g. a financial or other interest in an intervention or product similar to the intervention being studied).

A procedure should be established concerning the requirements for candidacy, including an outline of the duties and responsibilities of DSMB members.

Procedures for membership should include the following:

6.2.1.1 The procedure for selecting members, including the method for appointing a member (e.g. by application, committee or personal invitation).

6.2.1.2 The procedure for identifying conflicts of interest, and criteria for determining unacceptable conflicts of interest.

6.2.2 Terms of appointment

A procedure should be established identifying the terms of appointment for members of the DSMB, including

6.2.2.1 The duration of appointment.

6.2.2.2 The policy for renewal of an appointment.

6.2.2.3 The disqualification procedure.

6.2.2.4 The resignation procedure.

6.2.2.5 The replacement procedure.

6.2.3 Conditions of appointment

A procedure stating the conditions of appointment should be drawn up; it should include the requirements for:

6.2.3.1 A potential member to report in writing, at the time of candidacy, all potential or real conflicts of interest to the sponsor.

6.2.3.2 A member to be willing to publicize his/her full name, profession, and affiliation(s).

6.2.3.3 All reimbursement for work and expenses, if any, within or related to a DSMB to be recorded and made available to the public upon request.

6.2.3.4 A member to sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; this agreement should cover confidentiality requirements related to the intervention and protocol-related information as well as study results.

6.2.4 Offices

For a well-functioning DSMB, procedures for the Board's officers should be clearly defined. A description is required of: the officers within the DSMB (e.g. chairperson, secretary); the requirements for holding each office; the terms and conditions of each office; and the duties and responsibilities of each office (e.g. agenda, minutes, notification of recommendations). Procedures for selecting or appointing officers should be established.

6.2.5 Independent consultants

The sponsor may call upon, or establish, a standing list of independent consultants in accordance with the DSMB charter. Independent consultants provide special expertise to the DSMB; they may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities or special interest groups. For international studies, particularly those involving disease-endemic countries, efforts should be made to access expertise from countries or regions involved in the study, and there should be recognition that other expertise (e.g. anthropology or health policy) may be useful.

For studies which have mortality or major morbidity as endpoints, a medical monitor may be requested to review reports of serious

adverse events (SAEs) on an ongoing basis, in order to ensure good clinical care and identify early safety concerns. The medical monitor may be invited to report SAEs or other safety concerns at DSMB meetings.

Terms of reference for independent consultants and medical monitors should be established to identify the role of these persons vis-à-vis the DSMB and the data.

6.2.6 Conflict of interest

Procedures for reporting and addressing potential or real conflicts of interest for members and independent consultants should be clearly defined in the charter, as well as criteria for deciding whether a (potential) member or consultant has an unacceptable conflict of interest. The procedures should ensure the independence of DSMB members in decision-making (that is, in providing recommendations).

6.2.7 Education for DSMB members

The conditions of appointment should state the provisions made for training of DSMB members in the work of a DSMB. The training should include an introduction to the study the participants will be monitoring, and the charter for the DSMB on which they will be serving.

6.2.8 Staff

When appropriate, staff should be provided to support the DSMB's work. Measures to protect the confidentiality of the study and the patients/subjects should be defined for the staff.

6.2.9 Quorum requirements

The DSMB charter should establish specific quorum requirements for reviewing, and making recommendations on, the study, which should include:

6.2.9.1 The minimum number of members required to compose a quorum (e.g. more than half the members).

6.2.9.2 The professional qualifications required (e.g. physician, biostatistician, paramedic, ethics). A quorum should include at least one physician with experience in the medical field of concern, and one biostatistician.

6.2.10 Meeting requirements

The charter should specify the meetings to be held, including their expected frequency and venue. The charter should indicate whether the meetings will be held in person or by teleconference. Under exceptional circumstances, the DSMB may have to meet urgently or hold a teleconference within a short time period. Procedures for this should be described in the DSMB charter, under meeting requirements.

The meeting requirements should include the following:

6.2.10.1 Meetings should be planned in accordance with the DSMB charter.

6.2.10.2 DSMB members should be given enough time to review the materials for the meeting.

6.2.10.3 Minutes of the meeting should be documented, and finalized following an approval procedure.

6.2.10.4 Procedures for inviting the sponsor and/or investigator to the meeting should be outlined, including the measures used to ensure that the resulting recommendation is based fully on the independent decision-making of each member (e.g. the use of a closed session for discussion and arriving at a recommendation).

6.2.10.5 The procedure for inviting independent consultants to a meeting or to provide written comments should be defined, including the applicable confidentiality agreement.

6.2.11 Meeting procedures

Procedures for organization of the meetings should be developed in accordance with the meeting requirements.

6.2.11.1 Organizational meeting

This initial meeting should be attended by the DSMB members and representatives of the sponsor; members of the study staff and the investigator(s) may also be invited. The DSMB members should review and discuss the DSMB charter, including the role and responsibilities of the DSMB, the protocol safety monitoring plan, and the statistical methodology.

The DSMB should review the protocol, informed consent documents, the investigator's brochure, relevant literature(s), and other research-related document(s), posing any questions it has. The DSMB should also consider prior ethics committee(s) reviews, as well as the requirements of applicable laws and regulations. The statistical methodology described in the protocol and its role in the DSMB safety monitoring plan should be clarified at this initial meeting.

DSMB members should receive orientation regarding the procedures outlined in the charter, and training in relevant guidelines and SOPs. The DSMB may, in the context of this discussion, propose changes to the charter. The sponsor is responsible for final decisions relating to the charter. This organizational meeting takes place prior to finalization of the study protocol and review by the ethics committee(s).

6.2.11.2 Early safety review meeting

During the early stages of implementation of a study, a meeting may be held to review early safety information and factors relating to quality of conduct of the study.

6.2.11.3 Periodic review meetings

The expected frequency of these meetings should be specified. The DSMB charter should indicate whether the meetings are to be held in person or by teleconference. The meetings should review the efficacy and/or safety data generated during this period, and should include a progress report from the investigator, serious adverse events reports, and cumulative safety data. The DSMB should take into account the quality of conduct of the study and the accuracy of the data.

The agenda for each DSMB meeting should be established based on the discussions and recommendations from previous meetings as well as according to events in, or related to, the study that may have occurred since the previous meeting. Procedures regarding the: responsibility for drafting, reviewing, and approving the agenda; issues to be reviewed; consultants and other participants; and the sequence of open and closed sessions (see section 6.2.12), should be designed in advance.

The DSMB charter should indicate if the DSMB will have access to the monitors' and auditors' reports as well as other documents relating to quality assurance activities.

The DSMB charter should indicate when and how to break the code during the course of the study. A third party data analyst (e.g. an independent biostatistician) might provide a breakdown of adverse events to the DSMB members. When significant trends in the data require further interpretation, the DSMB may request unblinding of the data. In these cases, it may only be immediately necessary to unblind the statistician or epidemiologist, for example, and not all the DSMB members. The unblinded person then reports to the other members if there is cause for concern. The unblinding procedures should be defined in advance and supported by documentation which indicates who has access to the unblinded data.

When appropriate, a mechanism should be developed for timely reporting and assessment of serious adverse events, between regularly scheduled meetings of the DSMB, to ensure that participants are not put at undue risk. Designating an independent medical safety monitor to fulfil this responsibility is an effective approach.

6.2.11.4 Final study closeout meeting

At the termination or conclusion of a study, the DSMB may meet to consider the efficacy and/or safety data generated from the study and provide any final recommendation to the sponsor.

A final assessment report can be considered.

6.2.12 Format of meetings

The DSMB should ensure confidentiality and proper communication to enhance the integrity and credibility of the study. It is recommended that each DSMB meeting be divided into two sessions: an open session and a closed session. This will enable the DSMB to interact with groups and individuals who assume responsibilities for the study while ensuring the independence and integrity of the Board's recommendation.

6.2.12.1 Open session

The DSMB may request the at' ıdance of the study team, steering committee, investigator(s) and/or independent consultant(s) to provide specific clarification or respond to issues that have arisen. Open session discussion should focus on the conduct and progress of the study, and pay special attention to the pooled safety and efficacy data.

6.2.12.2 Closed session

Only DSMB members should be present at the closed session. In this session, the DSMB should review the efficacy and safety data, at times in unblinded format. The DSMB should consider the data in relation to the conduct and progress of the study, and the study protocol. The DSMB should also decide, in closed session, on the written recommendation it will present to the sponsor.

6.2.13 DSMB review of the sponsor's report

The sponsor should report the safety and efficacy data, as well as other relevant study information, to the DSMB for its review. The sponsor's report to the DSMB is often provided in two parts: an open part and a closed part. The full report should be made available to DSMB members in advance (at least one week) of the meeting.

The contents of the report are determined by the DSMB charter and discussed in advance during the organizational meeting. The charter should specify who will prepare and provide the open part of the report, and who will prepare and provide the closed part.

The open and closed parts can be provided by two separate parties.

6.2.13.1 Open part

The open part of the sponsor's report should include blinded and non-confidential data, e.g. participant recruitment, baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, protocol compliance, problems encountered in the conduct of the protocol, and any new information/publications that bear on the study.

6.2.13.2 Closed part

The closed part of the sponsor's report may include unblinded data and confidential information, as applicable, e.g. unblinded analyses of primary and secondary endpoints, analysis of SAEs for severity and seriousness, analyses of laboratory data, summary of global and site-specific safety data, and any other pertinent information from the sponsor or study sites during this or a previous confidential meeting.

In blinded studies, the charter should outline whether and when the DSMB will receive completely or partially unblinded data. The charter should outline who is responsible for unblinding the data, the procedure for unblinding the data, and all parties who will have access to unblinded data.

6.2.14 Arriving at recommendations

In advising on the continuation (without changes to the protocol or its implementation), modification, suspension, or termination of the study, the DSMB needs to take into account prior reviews, the requirements of applicable laws and regulations, and the scientific and ethical appropriateness of continuing the study. Statistical analysis may provide evidence that justifies a recommendation for continuation, modification, suspension, or termination of the study, but consideration of all available data from the study or relevant information external to the study may be necessary to arrive at a more complete judgement. A DSMB should also take the following into consideration in its decision-making process:

6.2.14.1 A member should excuse himself/herself from the meeting during the decision procedure in case of conflict of interest; any potential conflict of interest should be disclosed to the chairperson prior to the meeting and recorded in the minutes.

6.2.14.2 Recommendations should only be made at meetings where a quorum (as stipulated in the charter) is present.

6.2.14.3 The documents required for a full review of the study should be available to each member, and the relevant elements mentioned in the safety monitoring plan should be considered before a recommendation is made.

6.2.14.4 Only DSMB members who participate in the review should be involved in making a recommendation.

6.2.14.5 There should be a predefined method for arriving at a recommendation (e.g. by consensus, by vote). It is recommended that recommendations be arrived at through consensus, wherever possible; when a consensus appears unlikely, it is recommended that the DSMB votes.

6.2.14.6 A recommendation to modify, suspend, or terminate the study should be supported by clearly stated reasons. If the recommendation is based on a vote, dissenting members should have the option to append a minority view to the majority opinion.

6.2.15 Minutes of the DSMB meeting

An appropriately detailed summary of the DSMB's discussions should be recorded, with the recommendation clearly documented.

6.2.15.1 Minutes of open sessions should describe the proceedings of these sessions at DSMB meetings, and summarize all DSMB findings, including the recommendation to continue, modify, suspend, or terminate the study. These minutes should not contain any unblinded information

because they may be distributed to the sponsor, investigator(s), and oversight groups.

6.2.15.2 Minutes of closed session(s) should describe the proceedings of both the open and closed sessions. This part of the minutes should only be distributed to members of the DSMB, unless otherwise specified in the charter.

6.2.15.3 Copies of the minutes of the open sessions should be sent to the sponsor, who will distribute them and/or the recommendation further, in accordance with the DSMB charter. Copies of the minutes of closed sessions should be forwarded to the sponsor at the end of the study, or when indicated in the DSMB charter.

6.2.16 Communicating the DSMB recommendation

The recommendation should be communicated in writing to the sponsor within a predefined period, according to the DSMB charter and its procedures. This communication should include, but is not limited to, the following:

6.2.16.1 The exact title of the study reviewed.

6.2.16.2 Clearly identified date and version/number of the study.

6.2.16.3 The name and title of the principal investigator(s) or the coordinating investigator, when applicable.

6.2.16.4 The name of the study site(s).

6.2.16.5 The name (or some identifier) of the DSMB providing the recommendation.

6.2.16.6 The date and place when/where the recommendation was made.

6.2.16.7 A clear statement of the recommendation. In cases where the recommendation suggests modification, suspension, or termination of the study, clearly stated reason(s) for this need to be provided.

6.2.16.8 The signature (dated) of the chairperson (or other authorized person) of the DSMB.

6.2.13.9 Documentation of the delivery and receipt of the recommendation and its acknowledgement by the sponsor.

6.2.17 Distribution of the DSMB recommendation

The sponsor should establish a procedure for receiving and distributing the recommendation of a DSMB. The sponsor is responsible for distributing the recommendation, in a timely manner, to the steering committee, investigator(s), ethics committee(s), and regulatory authority(ies) involved in the study. Procedures for implementing the recommendation of the DSMB also need to be considered in advance.

6.2.18 Documentation and archiving

All documentation and communications of a DSMB should be dated, filed, and archived according to written procedures. A DSMB should develop an SOP to define the archival and access procedures (including naming the persons responsible for archiving the materials and those authorized to access the archived materials) for the various documents, files, and archives. The SOPs should include special precautions concerning the filing and archiving of randomization codes or lists. The documents should be archived for the duration of study. At the closure of the study, the archived materials should be forwarded to the sponsor.

Documents that should be filed and archived include, but are not limited to:

6.2.18.1 The DSMB charter.

6.2.18.2 The curricula vitae of all DSMB members.

6.2.18.3 A signed and dated statement from each DSMB member indicating that he/she understands his/her responsibilities and that he/she has no interests that

conflict with the objective performance of his/her duties and responsibilities as a member of the DSMB.

6.2.18.4 A record of all income and expenses of the DSMB, including payments and reimbursements made to the DSMB members.

6.2.18.5 The agendas of DSMB meetings.

6.2.18.6 The minutes of DSMB meetings.

6.2.18.7 A copy of all materials received by the DSMB, including the sponsor's reports.

6.2.18.8 A copy of the recommendation(s) provided by the DSMB to the sponsor.

6.2.18.9 A copy of all official DSMB correspondence.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these guidelines. The terms may have different meanings in other contexts.

Blinded/unblinded

Data (or their format/presentation) are considered 'blinded' when those with access to the data are not informed of the significant characteristics associated with them. Often this refers to identification of the intervention associated with the data. Data (or their format/presentation) are considered 'unblinded' when those with access to them are informed of the significant characteristics (e.g. intervention) to which the data are associated.

Charter

A document prepared by the sponsor which establishes the role and responsibilities of the DSMB vis-à-vis the sponsor and other parties engaged in the study.

Conflict of interest

A conflict of interest arises when a member(s) of the DSMB holds interests with respect to specific applications for review that may jeopardize his/her (their) ability to provide a free and independent evaluation of the research. Conflicts of interests may arise when a DSMB member has financial, institutional, or social ties to the research.

Data & Safety Monitoring Board (DSMB)

An independent committee established by the sponsor to assess, at intervals, the ongoing scientific and ethical integrity of a study by reviewing and evaluating (unblinded) data and reports at regular intervals. The DSMB provides non-bonding recommendations to the sponsor regarding study modification, suspension, or termination. There is no fixed or harmonized international name for committees performing this function. Other names for

committees performing the same or similar functions include, but are not limited to: Data Monitoring Committee (DMC), Independent Data Monitoring Committee (IDMC), Monitoring Committee (MC), Data & Ethics Monitoring Committee (DEMC), Safety Monitoring Committee, Study Monitoring Committee.

Ethics committee

An independent body (an institutional, regional, national, or supranational board or committee) established to review independently proposed and ongoing research. Such committees are also known variously as Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), Research Ethics Boards (REBs), Research Ethics Committees, and other designations.

Investigator

A qualified scientist who takes on the scientific and ethical responsibility, either on his/her own behalf or on behalf of an organization/firm, for the ethical and scientific integrity of a research project at a specific site or group of sites. In some instances, a coordinating or principal investigator may be appointed as the responsible leader of a team of co-investigators.

Protocol

A document that provides the background, rationale, and objective(s) of a health research project, and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.

Recommendation

Non-binding decisions provided by the DSMB to the sponsor concerning the Board's scientific and ethical appreciation of the study and regarding the continuation, modification, suspension, or termination of the study following review of the accumulated safety and efficacy data.

Research participant

An individual who participates in a research project, either as the direct recipient of an intervention (for example, study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, a person with a condition unrelated to the research being carried out and who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

Standard operating procedures (SOPs)

Detailed, written instructions to achieve uniformity of performance of a specific function.

Sponsor

An individual, company, institution, or organization that, either singularly or collectively, takes responsibility for the initiation, management, and/or financing of a health research project. The sponsor of a study may be composed of a number of individuals, companies, institutions, or organizations that share the responsibilities of the study. In this case, it is important that the protocol clearly defines how the sponsor responsibilities are distributed, the individual(s) or organization(s) responsible for establishing the DSMB, and to whom the DSMB reports.

SUPPORTING DOCUMENTS

Council for International Organizations of Medical Sciences (CIOMS). *International ethical guidelines for biomedical research involving human subjects*, revised ed. Geneva, CIOMS, 2002 (www.cioms.ch).

Department of Health, Education, and Welfare, Office of the Secretary, Protection of Human Subjects. *Belmont report: Ethical principles and guidelines for the protection of human subjects of research. Report of the National Committee for the Protection of Human Subjects of Biomedical and Behavioural Research*. DHEW publication no. (OS) 78-0013 and no. (OS) 78-0014, 18 April 1979.

European Commission, Enterprise Directorate-General. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. Brussels, ENTR/F2/BL D(2003), April 2004 (final).

Frank D et al. Sponsorship, authorship, and accountability. *The New England Journal of Medicine*, 2001, 345:825-7.

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *E9 statistical principles for clinical trials* http://www.ich.org/MediaServer.jser?@_ID=485&@_MODE=GLB)

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *E10 Choice of control group and related issued in clinical trials* (http://www.ich.org/MediaServer.jser?@_ID=486&@_MODE=GLB)

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for guidance on good clinical practice*.1 May 1996 (http://www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB)

Mitsuishi T, Nudeshima J, Kurihara C. *Proposal of a draft human research participants protection bill*. Rinsho Hyoka (Clinical Evaluation), 2003, 30(2,3):369-95.

National Cancer Institute (NCI), National Institutes of Health (NIH), USA. *Policy of the National Cancer Institute for the data and safety monitoring of clinical trials*. Approved by the NCI Executive Committee, 22 June 1999 (deainfo.nci.nih.gov/grantspolicies/datasafety.htm, accessed 14 October 2004).

National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH), USA. *Data and safety monitoring guidelines for NCCAM-supported clinical trials* (nccam.nih.gov/research/policies/datasafety/index.htm, page last modified 23 May 2002, accessed 14 October 2004).

National Institutes of Health (NIH), USA. *NIH Policy for data and safety monitoring*, 10 June 1998 (manuscript; grants1.nih.gov/grants/guide/notice-files/not98-084.html, accessed 14 October 2004).

Offen WW. Data monitoring committees (DMC). In: *Encyclopedia of biopharmaceutical statistics*, 2nd ed. Marcel-Dekker, 2002.

Ellenberg SE, Fleming TR, DeMets DL. *Data monitoring committees in clinical trials: a practical perspective*. New York, John Wiley & Sons Ltd., 2002.

US Food and Drug Administration. *Guidance for clinical trial sponsor on the establishment and operation of clinical trial data monitoring committees*. Rockville MD, FDA, 2001 (www.fda.gov/cber/gdlns/clindatmon.htm).

World Health Organization (WHO). Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Annex 3 in: *The use of essential drugs*, Sixth Report of the WHO Expert Committee. Geneva, World Health Organization, 1995.

World Health Organization (TDR/WHO). *Operational guidelines for ethics committees that review biomedical research*. Geneva, WHO/TDR, 2001 (TDR/PRD/ETHICS/2000.1: www.who.int/tdr/publications/publications/ethics.htm).

World Medical Association. *Declaration of Helsinki: Ethical principles for research involving human subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; the 48th General Assembly, Somerset West, Republic of South Africa, October 1996; the 52nd General Assembly, Edinburgh, Scotland, October 2000; Washington 2002; and Tokyo 2004
(www.wma.net/e/policy/b3.htm).

7 COMMITTEES

International Working Party

Francis P. Crawley (Chairman)
European Forum for Good Clinical Practice (EFGCP)

Dalia Y. Wolf
Harvard Medical School, USA

Vichai Chokevivat
Forum for Ethical Review Committees in Asia & Western Pacific (FERCAP)

Vasantha Muthuswamy
Indian Council of Medical Research (ICMR), India

Mary Ann D. Lansang
International Clinical Epidemiology Network (INCLEN)

Odette Morin
International Federation of Pharmaceutical Manufacturer's Associations (IFPMA)

Mehran Falsafi
Hoffmann-La Roche

Kenji Hirayama
Nagasaki University, Japan

Nilima Kshirsagar
Medical School, India

Anders Bjorkman
Karolinska Institute, Sweden

Nadia Tornieporth
GlaxoSmithKline Pharmaceuticals

François Chazelle
Merck

Angela Bowen
Western Institutional Review Board (WIRB), USA

Consultation partners

Olga Kubar
Forum for Ethics Committees in the Confederation of Independent States (FECCIS)

Chifumbe Chintu
Pan-African Bioethics Initiative (PABIN)

Dafna Feinholz
Foro Latino Americano de Comités de Éthica en Investigacion en Salud (FLACEIS)
[Latin American Forum of Ethics Committees in Health Research]

Henry Dinsdale
Forum for ERBs/IRBs in Canada & the United States (FOCUS)

Amy P. Paterson
National Institutes of Health, USA

Sighild Westman Naeser
Medical Products Agency, Sweden

Jean Saint-Pierre
Health Canada

Tomasz Dyszynski
Polish Association for Good Clinical Practice

David Borasky
Family Health International, USA

Melody Lin
Office for Human Research Protections

Charles S. Mgone
African Malaria Network Trust

Ron Warren
Western Institutional Review Board (WIRB), USA

Susan Trainor
Audit Working Party, European Forum for Good Clinical Practice

Delon Human
World Medical Association

Drue H. Barrett
Centers for Disease Control, USA

Ellen Gadbois
Department of Health and Human Services, USA

Walter L. Strauss
Merck Research Laboratories

Khazal Paradis
EuropaBio

Susan Ellenberg
Food and Drug Administration, USA

Robert Temple
Food and Drug Administration, USA

Caroline Loew
Pharmaceuticals Research and Manufacturers of America, USA

Danielle Grondin
International Office of Migration

Patrick Le Courtois
European Medicines Agency (EMEA)

Chantal Bélorgey
French Health Product Safety Agency (AFSSAPS)

Chieko Kurihara
Center for Life Sciences & Society, Japan

Dominique Sprumont
University of Neuchâtel, Switzerland

Greg Koski
Harvard University, USA

Secretariat

Juntra Karbwang, WHO/TDR (Project Coordinator)
Robert Ridley, WHO/TDR
Howard Engers, WHO/TDR
Fabio Zicker, WHO/TDR
Marie-Paule Kieny, WHO/Initiative for Vaccine Research (IVR)
Alex Capron, WHO/Department of Ethics, Trade, Human Rights and Health Law (ETH)

8 BACKGROUND

These Operational Guidelines were developed following requests from international and national clinical research organizations and researchers for specific guidance on data and safety monitoring boards (DSMBs). The guidelines have been developed against the background of WHO experience in the management and oversight of clinical research, with the support of an international working party of experts and broad international consultation.

The first draft of these Operational Guidelines was presented at the Steering Committee and Advisory Board Meeting of the Strategic Initiative for Developing Capacity in Ethical Review at the Western Institutional Review Board in Olympia, Washington, USA, in August 2003. This was followed by a meeting of international experts at WHO/TDR in October 2003. Revisions of the draft guidelines were widely circulated for comment throughout the international clinical research community.

Agencies and individuals within the United States Department of Health and Human Services were particularly helpful in providing expert advice based on extensive experience with the establishment and functioning of DSMBs. During 2004, the revised draft guidelines were presented and discussed at regional meetings in Asia, Africa, Latin America, Eastern Europe, the European Union, and North America. The draft guidelines were then reviewed for their applicability by the WHO/TDR Clinical Trials Monitors' Network.

These Operational Guidelines represent the first international guidance dedicated to the role and functions of DSMBs. As the number of clinical trials increases globally, alongside an increasing call for greater ethical and scientific oversight of clinical research, DSMBs are becoming an increasingly established part of clinical research, and their responsibilities are increasingly pushed to the fore. The objective of these Operational Guidelines is to clarify the role and responsibilities of DSMBs based on an international reference point for constitution and function.

Comments and suggestions on all aspects of these Operational Guidelines are welcome for consideration in future revisions of this document. Please correspond with:

Dr Juntra Karbwang
Clinical Coordinator
TDR
World Health Organization
CH-1211 Geneva 27
Switzerland

Tel (41) 22 791 3867/8
Fax (41) 22 791 4774
E-mail: karbwangj@who.int
Website: http://www.who.int/tdr

International Ethical Guidelines for Biomedical Research Involving Human Subjects CIOMS 2002

International Ethical Guidelines for Biomedical Research Involving Human Subjects

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

CIOMS
Geneva
2002

CONTENTS

ACKNOWLEDGEMENTS

BACKGROUND
INTRODUCTION
INTERNATIONAL INSTRUMENTS AND GUIDELINES
GENERAL ETHICAL PRINCIPLES
PREAMBLE
THE GUIDELINES

Ethical justification and scientific validity of biomedical research involving human subjects

Ethical review

Ethical review committees
Ethical review of externally sponsored research

Informed consent

Individual informed consent
Obtaining informed consent: Essential information for prospective research subjects
Obtaining informed consent: Obligations of sponsors and investigators
Inducement to participate
Benefits and risks of study participation
Special limitations on risk when research involves individuals who are not capable of giving informed consent

* * * * *

Research in populations and communities with limited resources

* * * * *

Choice of control in clinical trials

Vulnerable groups

Equitable distribution of burdens and benefits in the selection of groups of subjects in research
Research involving vulnerable persons
Research involving children
Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

Women as research participants

Women as research participants
Pregnant women as research participants

* * * * *

Safeguarding confidentiality
Right of injured subjects to treatment and compensation
Strengthening capacity for ethical and scientific review and biomedical research
Ethical obligation of external sponsors to provide health-care services

Appendix 1: Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.
Appendix 2: The Declaration of Helsinki
Appendix 3: The phases of clinical trials of vaccines and drugs

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences (CIOMS) acknowledges the substantial financial contribution of the Joint United Nations Programme on HIV/AIDS (UNAIDS) to the preparation of the 2002 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. The World Health Organization in Geneva contributed generously also through the departments of Reproductive Health and Research, Essential Drugs and Medicines Policy, Vaccines and Biologicals, and HIV/AIDS/Sexually Transmitted Infections, as well as the Special Programme for Research and Training in Tropical Diseases. CIOMS was at all times free to avail of the services and facilities of WHO.

CIOMS acknowledges also with much appreciation the financial support to the project from the Government of Finland, the Government of Switzerland, the Swiss Academy of Medical Sciences, the Fogarty International Center at the National Institutes of Health, USA, and the Medical Research Council of the United Kingdom.

A number of institutions and organizations made valuable contributions by making their experts available at no cost to CIOMS for the three meetings held in relation to the revision project. This has been highly appreciated.

The task of finalizing the various drafts was in the hands of Professor Robert J. Levine, who served as consultant to the project and chair of the steering committee, and whose profound knowledge and understanding of the field is remarkable. He was ably assisted by Dr James Gallagher of the CIOMS secretariat, who managed the electronic discussion and endeavoured to accommodate or reflect in the text the numerous comments received. He also edited the final text. Special mention must be made of the informal drafting group set up to bring the influence of various cultures to bear on the process. The group, with two members of the CIOMS secretariat, met for five days in New York in January 2001 and continued for several months to interact electronically with one another and with the secretariat to prepare the third draft, posted on the CIOMS website in June 2001: Fernando Lolas Stepke (chair), John Bryant, Leonardo de Castro, Robert Levine, Ruth Macklin, and Godfrey Tangwa; the group continued from October 2001, together with Florencia Luna and Rodolfo Saracci, to cooperate in preparing the fourth draft. The contribution of this group was invaluable.

The interest and comments of the many organizations and individuals who responded to the several drafts of the guidelines posted on the CIOMS website or otherwise made available are gratefully acknowledged (Appendix 6)

At CIOMS, Sev Fluss was at all times ready and resourceful when consulted, with advice and constructive comment, and Mrs Kathryn Chalaby-Amsler responded most competently to the sometimes considerable demands made on her administrative and secretarial skills.

BACKGROUND

The Council for International Organizations of Medical Sciences (CIOMS) is an international nongovernmental organization in official relations with the World Health Organization (WHO). It was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949 with among its mandates that of maintaining collaborative relations with the United Nations and its specialized agencies, particularly with UNESCO and WHO.

CIOMS, in association with WHO, undertook its work on ethics in relation to biomedical research in the late 1970s. At that time, newly independent WHO Member States were setting up health-care systems. WHO was not then in a position to promote ethics as an aspect of health care or research. It was thus that CIOMS set out, in cooperation with WHO, to prepare guidelines " to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their

socioeconomic circumstances, laws and regulations, and executive and administrative arrangements". The World Medical Association had issued the original Declaration of Helsinki in 1964 and an amended version in 1975. The outcome of the CIOMS/WHO undertaking was, in 1982, *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

The period that followed saw the outbreak of the HIV/AIDS pandemic and proposals to undertake large-scale trials of vaccine and treatment drugs for the condition. These raised new ethical issues that had not been considered in the preparation of *Proposed Guidelines.* There were other factors also – rapid advances in medicine and biotechnology, changing research practices such as multinational field trials, experimentation involving vulnerable population groups, and also a changing view, in rich and poor countries, that research involving human subjects was largely beneficial and not threatening. The Declaration of Helsinki was revised twice in the 1980s – in 1983 and 1989. It was timely to revise and update the 1982 guidelines, and CIOMS, with the cooperation of WHO and its Global Programme on AIDS, undertook the task. The outcome was the issuing of two sets of guidelines: in 1991, *International Guidelines for Ethical Review of Epidemiological Studies*; and, in 1993, *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

After 1993, ethical issues arose for which the CIOMS Guidelines had no specific provision. They related mainly to controlled clinical trials, with external sponsors and investigators, carried out in low-resource countries and to the use of comparators other than an established effective intervention. The issue in question was the perceived need in those countries for low-cost, technologically appropriate, public-health solutions, and in particular for HIV/AIDS treatment drugs or vaccines that poorer countries could afford. Commentators took opposing sides on this issue. One advocated, for low-resource countries, trials of interventions that, while they might be less effective than the treatment available in the better-off countries, would be less expensive. All research efforts for public solutions appropriate to developing countries should not be rejected as unethical, they claimed. The research context should be considered. Local decision-making should be the norm. Paternalism on the part of the richer countries towards poorer countries should be avoided. The challenge was to encourage research for local solutions to the burden of disease in much of the world, while providing clear guidance on protecting against exploitation of vulnerable communities and individuals.

The other side argued that such trials constituted, or risked constituting, exploitation of poor countries by rich countries and were inherently unethical. Economic factors should not influence ethical considerations. It was within the capacity of rich countries or the pharmaceutical industry to make established effective treatment available for comparator purposes. Certain low-resource countries had already made available from their own resources established effective treatment for their HIV/AIDS patients.

This conflict complicated the revision and updating of the 1993 Guidelines. Ultimately, it became clear that the conflicting views could not be reconciled, though the proponents of the former view claimed that the new guidelines had built in effective safeguards against

exploitation. The commentary to the Guideline concerned (11) recognizes the unresolved, or unresolvable, conflict.

The revision/updating of the 1993 Guidelines began in December 1998, and a first draft prepared by the CIOMS consultant for the project was reviewed by the project steering committee, which met in May 1999. The committee proposed amendments and listed topics on which new or revised guidelines were indicated; it recommended papers to be commissioned on the topics, as well as authors and commentators, for presentation and discussion at a CIOMS interim consultation. It was considered that an interim consultation meeting, of members of the steering committee together with the authors of commissioned papers and designated commentators, followed by further redrafting and electronic distribution and feedback, would better serve the purpose of the project than the process originally envisaged, which had been to complete the revision in one further step. The consultation was accordingly organized for March 2000, in Geneva.

At the consultation, progress on the revision was reported and contentious matters reviewed. Eight commissioned papers previously distributed were presented, commented upon, and discussed. The work of the consultation continued with ad hoc electronic working groups over the following several weeks, and the outcome was made available for the preparation of the third draft. The material commissioned for the consultation was made the subject of a CIOMS publication: *Biomedical Research Ethics: Updating International Guidelines. A Consultation* (December 2000).

An informal redrafting group of eight, from Africa, Asia, Latin America, the United States and the CIOMS secretariat met in New York City in January 2001, and subsequently interacted electronically with one another and with the CIOMS secretariat. A revised draft was posted on the CIOMS website in June 2001 and otherwise widely distributed. Many organizations and individuals commented, some extensively, some critically. Views on certain positions, notably on placebo-controlled trials, were contradictory. For the subsequent revision two members were added to the redrafting group, from Europe and Latin America. The consequent draft was posted on the website in January 2002 in preparation for the CIOMS Conference in February/ March 2002

The CIOMS Conference was convened to discuss and, as far as possible, endorse a final draft to be submitted for final approval to the CIOMS Executive Committee. Besides representation of member organizations of CIOMS, participants included experts in ethics and research from all continents. They reviewed the draft guidelines seriatim and suggested modifications. Guideline 11, *Choice of control in clinical trials*, was redrafted at the conference in an effort to reduce disagreement. The redrafted text of that guideline was intensively discussed and generally well received. Some participants, however, continued to question the ethical acceptability of the exception to the general rule limiting the use of placebo to the conditions set out in the guideline; they argued that research subjects should not be exposed to risk of serious or irreversible harm when an established effective intervention could prevent such harm, and that such exposure could constitute exploitation. Ultimately, the commentary of Guideline 11 reflects the opposing positions

on use of a comparator other than an established effective intervention for control purposes.

The new text, the 2002 text, which supersedes that of 1993, consists of a statement of general ethical principles, a preamble and 21 guidelines, with an introduction and a brief account of earlier declarations and guidelines. Like the 1982 and 1993 Guidelines, the present publication is designed to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects

Comments on the Guidelines are welcome and should be addressed to the Secretary-General, Council for International Organizations of Medical Sciences, c/o World Health Organization, CH-1211 Geneva 27, Switzerland; or by e-mail to cioms@who.int

INTRODUCTION

This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences since 1982. Its scope and preparation reflect well the transformation that has occurred in the field of research ethics in the almost quarter century since CIOMS first undertook to make this contribution to medical sciences and the ethics of research. The CIOMS Guidelines, with their stated concern for the application of the Declaration of Helsinki in developing countries, necessarily reflect the conditions and the needs of biomedical research in those countries, and the implications for multinational or transnational research in which they may be partners.

An issue, mainly for those countries and perhaps less pertinent now than in the past, has been the extent to which ethical principles are considered universal or as culturally relative – the universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care. The Guidelines take the position that research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards.

Related to this issue is that of the human rights of research subjects, as well as of health professionals as researchers in a variety of sociocultural contexts, and the contribution that international human rights instruments can make in the application of the general principles of ethics to research involving human subjects. The issue concerns largely,

though not exclusively, two principles: respect for autonomy and protection of dependent or vulnerable persons and populations. In the preparation of the Guidelines the potential contribution in these respects of human rights instruments and norms was discussed, and the Guideline drafters have represented the views of commentators on safeguarding the corresponding rights of subjects.

Certain areas of research are not represented by specific guidelines. One such is human genetics. It is, however, considered in Guideline 18 Commentary under *Issues of confidentiality in genetics research.* The ethics of genetics research was the subject of a commissioned paper and commentary.

Another unrepresented area is research with products of conception (embryo and fetal research, and fetal tissue research). An attempt to craft a guideline on the topic proved unfeasible. At issue was the moral status of embryos and fetuses and the degree to which risks to the life or well-being of these entities are ethically permissible.

In relation to the use of comparators in controls, commentators have raised the the question of standard of care to be provided to a control group. They emphasize that standard of care refers to more than the comparator drug or other intervention, and that research subjects in the poorer countries do not usually enjoy the same standard of all-round care enjoyed by subjects in richer countries. This issue is not addressed specifically in the Guidelines.

In one respect the Guidelines depart from the terminology of the Declaration of Helsinki. 'Best current intervention' is the term most commonly used to describe the active comparator that is ethically preferred in controlled clinical trials. For many indications, however, there is more than one established 'current' intervention and expert clinicians do not agree on which is superior. In other circumstances in which there are several established 'current' interventions, some expert clinicians recognize one as superior to the rest; some commonly prescribe another because the superior intervention may be locally unavailable, for example, or prohibitively expensive or unsuited to the capability of particular patients to adhere to a complex and rigorous regimen. 'Established effective intervention' is the term used in Guideline 11 to refer to all such interventions, including the best and the various alternatives to the best. In some cases an ethical review committee may determine that it is ethically acceptable to use an established effective intervention as a comparator, even in cases where such an intervention is not considered the best current intervention.

The mere formulation of ethical guidelines for biomedical research involving human subjects will hardly resolve all the moral doubts that can arise in association with much research, but the Guidelines can at least draw the attention of sponsors, investigators and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of research, and thus conduce to high scientific and ethical standards of biomedical research.

INTERNATIONAL INSTRUMENTS AND GUIDELINES

The first international instrument on the ethics of medical research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians (the Doctors' Trial) who had conducted atrocious experiments on unconsenting prisoners and detainees during the second world war. The Code, designed to protect the integrity of the research subject, set out conditions for the ethical conduct of research involving human subjects, emphasizing their voluntary consent to research.

The Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations in 1948. To give the Declaration legal as well as moral force, the General Assembly adopted in 1966 the International Covenant on Civil and Political Rights. Article 7 of the Covenant states "*No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation*". It is through this statement that society expresses the fundamental human value that is held to govern all research involving human subjects – the protection of the rights and welfare of all human subjects of scientific experimentation.

The Declaration of Helsinki, issued by the World Medical Association in 1964, is the fundamental document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration, amended several times, most recently in 2000 (Appendix 2), is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and nonclinical biomedical research.

Since the publication of the CIOMS 1993 Guidelines, several international organizations have issued ethical guidance on clinical trials. This has included, from the World Health Organization, in 1995, *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products*; and from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in 1996, *Guideline on Good Clinical Practice*, designed to ensure that data generated from clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan and the United States of America. The Joint United Nations Programme on HIV/AIDS published in 2000 the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research*.

In 2001 the Council of Ministers of the European Union adopted a Directive on clinical trials, which will be binding in law in the countries of the Union from 2004. The Council of Europe, with more than 40 member States, is developing a Protocol on Biomedical Research, which will be an additional protocol to the Council's 1997 Convention on Human Rights and Biomedicine.

Not specifically concerned with biomedical research involving human subjects but clearly pertinent, as noted above, are international human rights instruments. These are mainly the Universal Declaration of Human Rights, which, particularly in its science provisions, was highly influenced by the Nuremberg Code; the International Covenant on Civil and Political Rights; and the International Covenant on Economic, Social and Cultural Rights. Since the Nuremberg experience, human rights law has expanded to include the protection of women (Convention on the Elimination of All Forms of Discrimination Against Women) and children (Convention on the Rights of the Child). These and other such international instruments endorse in terms of human rights the general ethical principles that underlie the CIOMS International Ethical Guidelines.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

Respect for persons incorporates at least two fundamental ethical considerations, namely:

a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and

b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence refers to the ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, ***nonmaleficence*** (do no harm).

Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to ***distributive justice***, which requires the equitable distribution of both the burdens and the benefits of

participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons.

Sponsors of research or investigators cannot, in general, be held accountable for unjust conditions where the research is conducted, but they must refrain from practices that are likely to worsen unjust conditions or contribute to new inequities. Neither should they take advantage of the relative inability of low-resource countries or vulnerable populations to protect their own interests, by conducting research inexpensively and avoiding complex regulatory systems of industrialized countries in order to develop products for the lucrative markets of those countries.

In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.

Justice requires also that the research be responsive to the health conditions or needs of vulnerable subjects. The subjects selected should be the least vulnerable necessary to accomplish the purposes of the research. Risk to vulnerable subjects is most easily justified when it arises from interventions or procedures that hold out for them the prospect of direct health-related benefit. Risk that does not hold out such prospect must be justified by the anticipated benefit to the population of which the individual research subject is representative.

PREAMBLE

The term "research" refers to a class of activity designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In the present context "research" includes both medical and behavioural studies pertaining to human health. Usually "research" is modified by the adjective "biomedical" to indicate its relation to health.

Progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes or epidemiological findings, and requires at some time research involving human subjects. The collection, analysis and interpretation

of information obtained from research involving human beings contribute significantly to the improvement of human health.

Research involving human subjects includes:

- studies of a physiological, biochemical or pathological process, or of the response to a specific intervention – whether physical, chemical or psychological – in healthy subjects or patients;

- controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;

- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and

- studies concerning human health-related behaviour in a variety of circumstances and environments.

Research involving human subjects may employ either observation or physical, chemical or psychological intervention; it may also either generate records or make use of existing records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in *International Guidelines for Ethical Review of Epidemiological Studies (CIOMS, 1991).*

The research may be concerned with the social environment, manipulating environmental factors in a way that could affect incidentally-exposed individuals. It is defined in broad terms in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for health-related purposes.

Biomedical research with human subjects is to be distinguished from the practice of medicine, public health and other forms of health care, which is designed to contribute directly to the health of individuals or communities. Prospective subjects may find it confusing when research and practice are to be conducted simultaneously, as when research is designed to obtain new information about the efficacy of a drug or other therapeutic, diagnostic or preventive modality.

As stated in Paragraph 32 of the Declaration of Helsinki, "In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and,

where appropriate, published. The other relevant guidelines of this Declaration should be followed."

Professionals whose roles combine investigation and treatment have a special obligation to protect the rights and welfare of the patient-subjects. An investigator who agrees to act as physician-investigator undertakes some or all of the legal and ethical responsibilities of the subject's primary-care physician. In such a case, if the subject withdraws from the research owing to complications related to the research or in the exercise of the right to withdraw without loss of benefit, the physician has an obligation to continue to provide medical care, or to see that the subject receives the necessary care in the health-care system, or to offer assistance in finding another physician.

Research with human subjects should be carried out only by, or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states: the aim of the research; the reasons for proposing that it involve human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators.

New vaccines and medicinal drugs, before being approved for general use, must be tested on human subjects in clinical trials; such trials constitute a substantial part of all research involving human subjects.

THE GUIDELINES

Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

Commentary on Guideline 1

Among the essential features of ethically justified research involving human subjects, including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research protocol submitted for review and clearance to scientific and ethical review committees (Appendix I).

Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: *Ethical review committees* and *Ethical review of externally sponsored research. O*ther ethical aspects of research are discussed in the remaining guidelines and their commentaries. The protocol designed for submission for review and clearance to scientific and ethical review committees should include, when relevant, the items specified in Appendix I, and should be carefully followed in conducting the research.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

Commentary on Guideline 2

Ethical review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be offered or accepted for a review committee`s approval or clearance of a protocol.

Scientific review. According to the Declaration of Helsinki (*Paragraph 11*), medical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where indicated, animal experimentation.

Scientific review must consider, inter alia, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary.

Ethical review. The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. Scientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is ipso facto unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects` and researchers` time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound. Also, it considers provisions for monitoring of data and safety.

If the ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, it should then consider whether any known or possible risks to the subjects are justified by the expected benefits, direct or indirect, and whether the proposed research methods will minimize harm and maximize benefit. (See Guideline 8: *Benefits and risks of study participation.)* If the proposal is sound and the balance of risks to anticipated benefits is reasonable, the committee should then determine whether the procedures proposed for obtaining informed consent are satisfactory and those proposed for the selection of subjects are equitable.

Ethical review of emergency compassionate use of an investigational therapy. In some countries, drug regulatory authorities require that the so-called compassionate or humanitarian use of an investigational treatment be reviewed by an ethical review committee as though it were research. Exceptionally, a physician may undertake the compassionate use of an investigational therapy before obtaining the approval or clearance of an ethical review committee, provided three criteria are met: a patient needs emergency treatment, there is some evidence of possible effectiveness of the investigational treatment, and there is no other treatment available that is known to be equally effective or superior. Informed consent should be obtained according to the legal requirements and cultural standards of the community in which the intervention is carried out. Within one week the physician must report to the ethical review committee the details of the case and the action taken, and an independent health-care professional must confirm in writing to the ethical review committee the treating physician's judgment that the use of the investigational intervention was justified according to the three specified criteria. (See also Guideline 13 Commentary section: *Other vulnerable groups.)*

National (centralized) or local review. Ethical review committees may be created under the aegis of national or local health administrations, national (or centralized) medical research councils or other nationally representative bodies. In a highly centralized administration a national, or centralized, review committee may be constituted for both the scientific and the ethical review of research protocols. In countries where medical research is not centrally administered, ethical review is more effectively and conveniently

undertaken at a local or regional level. The authority of a local ethical review committee may be confined to a single institution or may extend to all institutions in which biomedical research is carried out within a defined geographical area. The basic responsibilities of ethical review committees are:

- to determine that all proposed interventions, particularly the administration of drugs and vaccines or the use of medical devices or procedures under development, are acceptably safe to be undertaken in humans or to verify that another competent expert body has done so;
- to determine that the proposed research is scientifically sound or to verify that another competent expert body has done so;
- to ensure that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice;
- to consider the qualifications of the investigators, including education in the principles of research practice, and the conditions of the research site with a view to ensuring the safe conduct of the trial; and
- to keep records of decisions and to take measures to follow up on the conduct of ongoing research projects.

Committee membership. National or local ethical review committees should be so composed as to be able to provide complete and adequate review of the research proposals submitted to them. It is generally presumed that their membership should include physicians, scientists and other professionals such as nurses, lawyers, ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community and to ensure that the rights of the research subjects will be respected. They should include both men and women. When uneducated or illiterate persons form the focus of a study they should also be considered for membership or invited to be represented and have their views expressed.

A number of members should be replaced periodically with the aim of blending the advantages of experience with those of fresh perspectives.

A national or local ethical review committee responsible for reviewing and approving proposals for externally sponsored research should have among its members or consultants persons who are thoroughly familiar with the customs and traditions of the population or community concerned and sensitive to issues of human dignity.

Committees that often review research proposals directed at specific diseases or impairments, such as HIV/AIDS or paraplegia, should invite or hear the views of individuals or bodies representing patients with such diseases or impairments. Similarly, for research involving such subjects as children, students, elderly persons or employees, committees should invite or hear the views of their representatives or advocates.

To maintain the review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member`s objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, if to do so is clearly the appropriate action to take, either at the member`s own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members.

Multi-centre research. Some research projects are designed to be conducted in a number of centres in different communities or countries. Generally, to ensure that the results will be valid, the study must be conducted in an identical way at each centre. Such studies include clinical trials, research designed for the evaluation of health service programmes, and various kinds of epidemiological research. For such studies, local ethical or scientific review committees are not normally authorized to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. They should be fully empowered to prevent a study that they believe to be unethical. Moreover, changes that local review committees believe are necessary to protect the research subjects should be documented and reported to the research institution or sponsor responsible for the whole research programme for consideration and due action, to ensure that all other subjects can be protected and that the research will be valid across sites.

To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating centre or institution, or, failing this, explicit inter-centre comparability procedures must be introduced; changes made at some but not all will defeat the purpose of multi-centre research. For some multi-centre studies, scientific and ethical review may be facilitated by agreement among centres to accept the conclusions of a single review committee; its members could include a representative of the ethical review committee at each of the centres at which the research is to be conducted, as well as individuals competent to conduct scientific review. In other circumstances, a centralized review may be complemented by local review relating to the local participating investigators and institutions. The central committee could review the study from a scientific and ethical standpoint, and the local committees could verify the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance.

In a large multi-centre trial, individual investigators will not have authority to act independently, with regard to data analysis or to preparation and publication of manuscripts, for instance. Such a trial usually has a set of committees which operate under the direction of a steering committee and are responsible for such functions and decisions. The function of the ethical review committee in such cases is to review the relevant plans with the aim of avoiding abuses.

Sanctions. Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary. They should be required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies. Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards.

Sanctions imposed by governmental, institutional, professional or other authorities possessing disciplinary power should be employed as a last resort. Preferred methods of control include cultivation of an atmosphere of mutual trust, and education and support to promote in researchers and in sponsors the capacity for ethical conduct of research.

Should sanctions become necessary, they should be directed at the non-compliant researchers or sponsors. They may include fines or suspension of eligibility to receive research funding, to use investigational interventions, or to practise medicine. Unless there are persuasive reasons to do otherwise, editors should refuse to publish the results of research conducted unethically, and retract any articles that are subsequently found to contain falsified or fabricated data or to have been based on unethical research. Drug regulatory authorities should consider refusal to accept unethically obtained data submitted in support of an application for authorization to market a product. Such sanctions, however, may deprive of benefit not only the errant researcher or sponsor but also that segment of society intended to benefit from the research; such possible consequences merit careful consideration.

Potential conflicts of interest related to project support. Increasingly, biomedical studies receive funding from commercial firms. Such sponsors have good reasons to support research methods that are ethically and scientifically acceptable, but cases have arisen in which the conditions of funding could have introduced bias. It may happen that investigators have little or no input into trial design, limited access to the raw data, or limited participation in data interpretation, or that the results of a clinical trial may not be published if they are unfavourable to the sponsor's product. This risk of bias may also be associated with other sources of support, such as government or foundations. As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them. Investigators must also disclose potential or apparent conflicts of interest on their part to the ethical review committee or to other institutional committees designed to evaluate and manage such conflicts. Ethical review committees should therefore ensure that these conditions are met. See also *Multi-centre research*, above.

Guideline 3: Ethical review of externally sponsored research

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

Commentary on Guideline 3

Definition. The term *externally sponsored research* refers to research undertaken in a host country but sponsored, financed, and sometimes wholly or partly carried out by an external international or national organization or pharmaceutical company with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country.

Ethical and scientific review. Committees in both the country of the sponsor and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards. As far as possible, there must be assurance that the review is independent and that there is no conflict of interest that might affect the judgement of members of the review committees in relation to any aspect of the research. When the external sponsor is an international organization, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards.

Committees in the external sponsoring country or international organization have a special responsibility to determine whether the scientific methods are sound and suitable to the aims of the research; whether the drugs, vaccines, devices or procedures to be studied meet adequate standards of safety; whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsor or in another country; and whether the proposed research is in compliance with the ethical standards of the external sponsoring country or international organization.

Committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country. The ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee in the host country, therefore, must have as either members or consultants persons with such understanding; it will then be in a favourable position to determine the acceptability of the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as of the means proposed to protect the welfare of the research subjects. Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects, and to advise on whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange and other customs and traditions.

When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol. In short, in respect of host countries either with developed capacity for independent ethical review or in which external sponsors and investigators are contributing substantially to such capacity, ethical review in the external, sponsoring country may be limited to ensuring compliance with broadly stated ethical standards. The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research; it is also likely to be in a better position to monitor compliance in the course of a study. However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

Commentary on Guideline 4

General considerations. Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy. As an additional safeguard, it must always be complemented by independent ethical review of research proposals. This safeguard of independent review is particularly important as many individuals are limited in their capacity to give adequate informed consent; they include young children, adults with severe mental or behavioural disorders, and persons who are unfamiliar with medical concepts and technology (See Guidelines 13, 14, 15).

Process. Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures.

Language. Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that suits the individual's level of understanding. The investigator must bear in mind that the prospective subject`s ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system. It depends also on the investigator's ability and willingness to communicate with patience and sensitivity.

Comprehension. The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood.

Documentation of consent. Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so. The ethical review committee may approve waiver of the requirement of a signed consent form if the research carries no more than minimal risk – that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination – and if the procedures to be used are only those for which signed consent forms are not customarily required outside the research context. Such waivers may also be approved when existence of a signed consent form would be an unjustified threat to the subject's confidentiality. In some cases, particularly when the information is complicated, it is advisable to give subjects information sheets to retain; these may resemble consent forms in all respects except that subjects are not required to sign them. Their wording should be cleared by the ethical review committee. When consent has been obtained orally, investigators are responsible for providing documentation or proof of consent.

Waiver of the consent requirement. Investigators should never initiate research involving human subjects without obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects' records), the ethical review committee may waive some or all of the elements of informed consent.

Renewing consent. When material changes occur in the conditions or the procedures of a study, and also periodically in long-term studies, the investigator should once again seek informed consent from the subjects. For example, new information may have come to light, either from the study or from other sources, about the risks or benefits of products being tested or about alternatives to them. Subjects should be given such information promptly. In many clinical trials, results are not disclosed to subjects and investigators until the study is concluded. This is ethically acceptable if an ethical review committee has approved their non-disclosure.

Cultural considerations. In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. In some populations the use of a number of local languages may complicate the communication of information to potential subjects and the ability of an investigator to ensure that they truly understand it. Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. Sponsors and investigators should develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process. Also, they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects. For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

Consent to use for research purposes biological materials (including genetic material) from subjects in clinical trials. Consent forms for the research protocol should include a separate section for clinical-trial subjects who are requested to provide their consent for the use of their biological specimens for research. Separate consent may be appropriate in some cases (e.g., if investigators are requesting permission to conduct basic research which is not a necessary part of the clinical trial), but not in others (e.g., the clinical trial requires the use of subjects' biological materials).

Use of medical records and biological specimens. Medical records and biological specimens taken in the course of clinical care may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed. Patients have a right to know that their records or specimens may be used for research. Refusal or reluctance of individuals to agree to participate would not be evidence of impracticability sufficient to warrant waiving informed consent. Records and specimens of individuals who have specifically rejected such uses in the past may be used only in the case of public health emergencies. (See Guideline 18 Commentary, *Confidentiality between physician and patient)*

Secondary use of research records or biological specimens. Investigators may want to use records or biological specimens that another investigator has used or collected for use, in another institution in the same or another country. This raises the issue of whether the records or specimens contain personal identifiers, or can be linked to such identifiers, and by whom. (See also Guideline 18: *Safeguarding confidentiality*) If informed consent or permission was required to authorize the original collection or use of such records or specimens for research purposes, secondary uses are generally constrained by the conditions specified in the original consent. Consequently, it is essential that the original consent process anticipate, to the extent that this is feasible, any foreseeable plans for future use of the records or specimens for research. Thus, in the original process of seeking informed consent a member of the research team should discuss with, and, when indicated, request the permission of, prospective subjects as to: i) whether there will or could be any secondary use and, if so, whether such secondary use will be limited with regard to the type of study that may be performed on such materials; ii) the conditions under which investigators will be required to contact the research subjects for additional authorization for secondary use; iii) the investigators' plans, if any, to destroy or to strip of personal identifiers the records or specimens; and iv) the rights of subjects to request destruction or anonymization of biological specimens or of records or parts of records that they might consider particularly sensitive, such as photographs, videotapes or audiotapes.

(See also Guidelines 5: *Obtaining informed consent: Essential information for prospective research subjects;* 6: *Obtaining informed consent: Obligations of sponsors and investigators;* and 7: *Inducement to participate.)*

Guideline 5: Obtaining informed consent: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. **that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;**

2. **that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;**

3. **the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;**

4. **for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;**

5. **the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;**

6. **whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;**

7. **that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;**

8. **that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);**

9. **any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;**

10. **the direct benefits, if any, expected to result to subjects from participating in the research**

11. **the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;**

12. **whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;**

13. **any currently available alternative interventions or courses of treatment;**

14. **the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;**

15. **the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;**

16. **policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;**

17. **the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;**

18. **the possible research uses, direct or secondary, of the subject`s medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);**

19. **whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);**

20. **whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;**

21. **whether the investigator is serving only as an investigator or as both investigator and the subject`s physician;**

22. **the extent of the investigator's responsibility to provide medical services to the participant;**

23. **that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.**

24. **in what way, and by what organization, the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);**

25. **whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;**

26. **that an ethical review committee has approved or cleared the research protocol.**

Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators

Sponsors and investigators have a duty to:

- **refrain from unjustified deception, undue influence, or intimidation;**
- **seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;**
- **as a general rule, obtain from each prospective subject a signed form as evidence of informed consent – investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, *Documentation of consent*);**
- **renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,**
- **renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.**

Commentary on Guideline 6

The investigator is responsible for ensuring the adequacy of informed consent from each subject. The person obtaining informed consent should be knowledgeable about the research and capable of answering questions from prospective subjects. Investigators in charge of the study must make themselves available to answer questions at the request of subjects. Any restrictions on the subject's opportunity to ask questions and receive answers before or during the research undermines the validity of the informed consent.

In some types of research, potential subjects should receive counselling about risks of acquiring a disease unless they take precautions. This is especially true of HIV/AIDS vaccine research (UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research, Guidance Point 14).*

Withholding information and deception. Sometimes, to ensure the validity of research, investigators withhold certain information in the consent process. In biomedical research, this typically takes the form of withholding information about the purpose of specific procedures. For example, subjects in clinical trials are often not told the purpose of tests performed to monitor their compliance with the protocol, since if they knew their compliance was being monitored they might modify their behaviour and hence invalidate results. In most such cases, the prospective subjects are asked to consent to remain uninformed of the purpose of some procedures until the research is completed; after the

conclusion of the study they are given the omitted information. In other cases, because a request for permission to withhold some information would jeopardize the validity of the research, subjects are not told that some information has been withheld until the research has been completed. Any such procedure must receive the explicit approval of the ethical review committee.

Active deception of subjects is considerably more controversial than simply withholding certain information. Lying to subjects is a tactic not commonly employed in biomedical research. Social and behavioural scientists, however, sometimes deliberately misinform subjects to study their attitudes and behaviour. For example, scientists have pretended to be patients to study the behaviour of health-care professionals and patients in their natural settings.

Some people maintain that active deception is never permissible. Others would permit it in certain circumstances. Deception is not permissible, however, in cases in which the deception itself would disguise the possibility of the subject being exposed to more than minimal risk. When deception is deemed indispensable to the methods of a study the investigators must demonstrate to an ethical review committee that no other research method would suffice; that significant advances could result from the research; and that nothing has been withheld that, if divulged, would cause a reasonable person to refuse to participate. The ethical review committee should determine the consequences for the subject of being deceived, and whether and how deceived subjects should be informed of the deception upon completion of the research. Such informing, commonly called "debriefing", ordinarily entails explaining the reasons for the deception. A subject who disapproves of having been deceived should be offered an opportunity to refuse to allow the investigator to use information thus obtained. Investigators and ethical review committees should be aware that deceiving research subjects may wrong them as well as harm them; subjects may resent not having been informed when they learn that they have participated in a study under false pretences. In some studies there may be justification for deceiving persons other than the subjects by either withholding or disguising elements of information. Such tactics are often proposed, for example, for studies of the abuse of spouses or children. An ethical review committee must review and approve all proposals to deceive persons other than the subjects. Subjects are entitled to prompt and honest answers to their questions; the ethical review committee must determine for each study whether others who are to be deceived are similarly entitled.

Intimidation and undue influence. Intimidation in any form invalidates informed consent. Prospective subjects who are patients often depend for medical care upon the physician/investigator, who consequently has a certain credibility in their eyes, and whose influence over them may be considerable, particularly if the study protocol has a therapeutic component. They may fear, for example, that refusal to participate would damage the therapeutic relationship or result in the withholding of health services. The physician/investigator must assure them that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation the ethical review committee should consider whether a neutral third party should seek informed consent.

The prospective subject must not be exposed to undue influence. The borderline between justifiable persuasion and undue influence is imprecise, however. The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject's decision. (See also Guideline 4: *Individual informed consent.)*

Risks. Investigators should be completely objective in discussing the details of the experimental intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In complex research projects it may be neither feasible nor desirable to inform prospective participants fully about every possible risk. They must, however, be informed of all risks that a 'reasonable person' would consider material to making a decision about whether to participate, including risks to a spouse or partner associated with trials of, for example, psychotropic or genital-tract medicaments. (See also Guideline 8 Commentary, *Risks to groups of persons.*)

Exception to the requirement for informed consent in studies of emergency situations in which the researcher anticipates that many subjects will be unable to consent. Research protocols are sometimes designed to address conditions occurring suddenly and rendering the patients/subjects incapable of giving informed consent. Examples are head trauma, cardiopulmonary arrest and stroke. The investigation cannot be done with patients who can give informed consent in time and there may not be time to locate a person having the authority to give permission. In such circumstances it is often necessary to proceed with the research interventions very soon after the onset of the condition in order to evaluate an investigational treatment or develop the desired knowledge. As this class of emergency exception can be anticipated, the researcher must secure the review and approval of an ethical review committee before initiating the study. If possible, an attempt should be made to identify a population that is likely to develop the condition to be studied. This can be done readily, for example, if the condition is one that recurs periodically in individuals; examples include grand mal seizures and alcohol binges. In such cases, prospective subjects should be contacted while fully capable of informed consent, and invited to consent to their involvement as research subjects during future periods of incapacitation. If they are patients of an independent physician who is also the physician-researcher, the physician should likewise seek their consent while they are fully capable of informed consent. In all cases in which approved research has begun without prior consent of patients/subjects incapable of giving informed consent because of suddenly occurring conditions, they should be given all relevant information as soon as they are in a state to receive it, and their consent to continued participation should be obtained as soon as is reasonably possible.

Before proceeding without prior informed consent, the investigator must make reasonable efforts to locate an individual who has the authority to give permission on behalf of an incapacitated patient. If such a person can be located and refuses to give permission, the patient may not be enrolled as a subject. The risks of all interventions and procedures will be justified as required by Guideline 9 (*Special limitations on risks when research involves individuals who are not capable of giving consent).* The researcher and the ethical review committee should agree to a maximum time of involvement of an

individual without obtaining either the individual's informed consent or authorization according to the applicable legal system if the person is not able to give consent. If by that time the researcher has not obtained either consent or permission – owing either to a failure to contact a representative or to a refusal of either the patient or the person or body authorized to give permission – the participation of the patient as a subject must be discontinued. The patient or the person or body providing authorization should be offered an opportunity to forbid the use of data derived from participation of the patient as a subject without consent or permission.

Where appropriate, plans to conduct emergency research without prior consent of the subjects should be publicized within the community in which it will be carried out. In the design and conduct of the research, the ethical review committee, the investigators and the sponsors should be responsive to the concerns of the community. If there is cause for concern about the acceptability of the research in the community, there should be a formal consultation with representatives designated by the community. The research should not be carried out if it does not have substantial support in the community concerned. (See Guideline 8 Commentary, *Risks to groups of persons*.)

Exception to the requirement of informed consent for inclusion in clinical trials of persons rendered incapable of informed consent by an acute condition. Certain patients with an acute condition that renders them incapable of giving informed consent may be eligible for inclusion in a clinical trial in which the majority of prospective subjects will be capable of informed consent. Such a trial would relate to a new treatment for an acute condition such as sepsis, stroke or myocardial infarction. The investigational treatment would hold out the prospect of direct benefit and would be justified accordingly, though the investigation might involve certain procedures or interventions that were not of direct benefit but carried no more than minimal risk; an example would be the process of randomization or the collection of additional blood for research purposes. For such cases the initial protocol submitted for approval to the ethical review committee should anticipate that some patients may be incapable of consent, and should propose for such patients a form of proxy consent, such as permission of the responsible relative. When the ethical review committee has approved or cleared such a protocol, an investigator may seek the permission of the responsible relative and enrol such a patient.

Guideline 7: Inducement to participate

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better

judgment ("undue inducement"). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

Commentary on Guideline 7

Acceptable recompense. Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research may also receive a small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

Unacceptable recompense. Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; local ethical review committees may find such inducements acceptable. Monetary and in-kind recompense must, therefore, be evaluated in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances. When research interventions or procedures that do not hold out the prospect of direct benefit present more than minimal risk, all parties involved in the research – sponsors, investigators and ethical review committees – in both funding and host countries should be careful to avoid undue material inducement.

Incompetent persons. Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

Withdrawal from a study. A subject who withdraws from research for reasons related to the study, such as unacceptable side-effects of a study drug, or who is withdrawn on health grounds, should be paid or recompensed as if full participation had taken place. A subject who withdraws for any other reason should be paid in proportion to the amount of participation. An investigator who must remove a subject from the study for wilful noncompliance is entitled to withhold part or all of the payment.

Guideline 8: Benefits and risks of study participation

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

- **Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject.**

- **Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.**

Commentary on Guideline 8

The Declaration of Helsinki in several paragraphs deals with the well-being of research subjects and the avoidance of risk. Thus, considerations related to the well-being of the human subject should take precedence over the interests of science and society *(Paragraph 5)*; clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk (*Paragraph 11*); every project should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others (*Paragraph 16*); physician-researchers must be confident that the risks involved have been adequately assessed and can be satisfactorily managed (*Paragraph 17*); and the risks and burdens to the subject must be minimized, and reasonable in relation to the importance of the objective or the knowledge to be gained (*Paragraph 18*).

Biomedical research often employs a variety of interventions of which some hold out the prospect of direct therapeutic benefit (beneficial interventions) and others are administered solely to answer the research question (non-beneficial interventions). Beneficial interventions are justified as they are in medical practice by the expectation that they will be at least as advantageous to the individuals concerned, in the light of both risks and benefits, as any available alternative. Non-beneficial interventions are assessed differently; they may be justified only by appeal to the knowledge to be gained. In assessing the risks and benefits that a protocol presents to a population, it is appropriate to consider the harm that could result from forgoing the research.

Paragraphs 5 and 18 of the Declaration of Helsinki do not preclude well-informed volunteers, capable of fully appreciating risks and benefits of an investigation, from participating in research for altruistic reasons or for modest remuneration.

Minimizing risk associated with participation in a randomized controlled trial. In randomized controlled trials subjects risk being allocated to receive the treatment that proves inferior. They are allocated by chance to one of two or more intervention arms and followed to a predetermined end-point. (Interventions are understood to include new or established therapies, diagnostic tests and preventive measures.) An intervention is evaluated by comparing it with another intervention (a control), which is ordinarily the best current method, selected from the safe and effective treatments available globally, unless some other control intervention such as placebo can be justified ethically (See Guideline 11).

To minimize risk when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator must not, for purposes of conducting the trial, withhold therapy that is known to be superior to the intervention being tested, unless the withholding can be justified by the standards set forth in Guideline 11. Also, the investigator must provide in the research protocol for the monitoring of research data by an independent board (Data and Safety Monitoring Board); one function of such a board is to protect the research subjects from previously unknown adverse reactions or unnecessarily prolonged exposure to an inferior therapy. Normally at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

Risks to groups of persons. Research in certain fields, such as epidemiology, genetics or sociology, may present risks to the interests of communities, societies, or racially or ethnically defined groups. Information might be published that could stigmatize a group or expose its members to discrimination. Such information, for example, could indicate, rightly or wrongly, that the group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or is particularly susceptible to certain genetic disorders. Plans to conduct such research should be sensitive to such considerations, to the need to maintain confidentiality during and after the study, and to the need to publish the resulting data in a manner that is respectful of the interests of all concerned, or in certain circumstances not to publish them. The ethical review committee should ensure that the interests of all concerned are given due consideration; often it will be advisable to have individual consent supplemented by community consultation.

[The ethical basis for the justification of risk is elaborated further in Guideline 9]

Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent

When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.

Commentary on Guideline 9

The low-risk standard: Certain individuals or groups may have limited capacity to give informed consent either because, as in the case of prisoners, their autonomy is limited, or because they have limited cognitive capacity. For research involving persons who are unable to consent, or whose capacity to make an informed choice may not fully meet the standard of informed consent, ethical review committees must distinguish between intervention risks that do not exceed those associated with routine medical or psychological examination of such persons and risks in excess of those.

When the risks of such interventions do not exceed those associated with routine medical or psychological examination of such persons, there is no requirement for special substantive or procedural protective measures apart from those generally required for all research involving members of the particular class of persons. When the risks are in excess of those, the ethical review committee must find: 1) that the research is designed to be responsive to the disease affecting the prospective subjects or to conditions to which they are particularly susceptible; 2) that the risks of the research interventions are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation; 3) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and 4) that the interventions are reasonably commensurate with the clinical interventions that the subjects have experienced or may be expected to experience in relation to the condition under investigation.

If such research subjects, including children, become capable of giving independent informed consent during the research, their consent to continued participation should be obtained.

There is no internationally agreed, precise definition of a "slight or minor increase" above the risks associated with routine medical or psychological examination of such persons. Its meaning is inferred from what various ethical review committees have reported as having met the standard. Examples include additional lumbar punctures or bone-marrow aspirations in children with conditions for which such examinations are regularly indicated in clinical practice. The requirement that the objective of the research be relevant to the disease or condition affecting the prospective subjects rules out the use of such interventions in healthy children.

The requirement that the research interventions be reasonably commensurate with clinical interventions that subjects may have experienced or are likely to experience for the condition under investigation is intended to enable them to draw on personal experience as they decide whether to accept or reject additional procedures for research purposes. Their choices will, therefore, be more informed even though they may not fully meet the standard of informed consent.

(See also Guidelines 4: *Individual informed consent*; 13: *Research involving vulnerable persons;* 14: *Research involving children;* and 15: *Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent.)*

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- **the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and**
- **any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.**

Commentary on Guideline 10

This guideline is concerned with countries or communities in which resources are limited to the extent that they are, or may be, vulnerable to exploitation by sponsors and investigators from the relatively wealthy countries and communities.

Responsiveness of research to health needs and priorities. The ethical requirement that research be responsive to the health needs of the population or community in which it is carried out calls for decisions on what is needed to fulfil the requirement. It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population. This is applicable especially to research conducted in countries where governments lack the resources to make such products or benefits widely available. Even when a product to be tested in a particular country is much cheaper than the standard treatment in some other countries, the government or individuals in that country may still be unable to afford it. If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical.

When an investigational intervention has important potential for health care in the host country, the negotiation that the sponsor should undertake to determine the practical implications of "responsiveness", as well as "reasonable availability", should include representatives of stakeholders in the host country; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups. The negotiation should cover the health-care infrastructure required for safe and rational use of the intervention, the likelihood of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when this economic information is not proprietary. In some cases, satisfactory discussion of the availability and distribution of successful products will necessarily engage international organizations, donor governments and bilateral agencies, international nongovernmental organizations, and the private sector. The development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of the research.

Additionally, if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the community or population until some time after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it.

For minor research studies and when the outcome is scientific knowledge rather than a commercial product, such complex planning or negotiation is rarely, if ever, needed. There must be assurance, however, that the scientific knowledge developed will be used for the benefit of the population.

Reasonable availability. The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.

In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community. This should not be construed as precluding studies designed to evaluate novel therapeutic concepts. As a rare exception, for example, research may be designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial effect in the treatment of a disease that occurs only in regions with extremely limited resources, and it could not be

carried out reasonably well in more developed communities. Such research may be justified ethically even if there is no plan in place to make a product available to the population of the host country or community at the conclusion of the preliminary phase of its development. If the concept is found to be valid, subsequent phases of the research could result in a product that could be made reasonably available at its conclusion.

(See also Guidelines 3: *Ethical review of externally sponsored research;* 12, *Equitable distribution of burdens and benefits;* 20: *Strengthening capacity for ethical and scientific review and biomedical research;* and 21: *Ethical obligation of external sponsors to provide health-care services.)*

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".

Placebo may be used:

- **when there is no established effective intervention;**
- **when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;**
- **when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.**

Commentary on Guideline 11

General considerations for controlled clinical trials. The design of trials of investigational diagnostic, therapeutic or preventive interventions raises interrelated scientific and ethical issues for sponsors, investigators and ethical review committees. To obtain reliable results, investigators must compare the effects of an investigational intervention on subjects assigned to the investigational arm (or arms) of a trial with the effects that a control intervention produces in subjects drawn from the same population and assigned to its control arm. Randomization is the preferred method for assigning subjects to the various arms of the clinical trial unless another method, such as historical or literature controls, can be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial.

A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. When the objective is to establish the effectiveness and safety of an investigational intervention, the use of a placebo control is often much more likely than that of an active control to produce a scientifically reliable result. In many cases the ability of a trial to distinguish effective from ineffective interventions (its assay sensitivity) cannot be assured unless the control is a placebo. If, however, an effect of using a placebo would be to deprive subjects in the control arm of an established effective intervention, and thereby to expose them to serious harm, particularly if it is irreversible, it would obviously be unethical to use a placebo.

Placebo control in the absence of a current effective alternative. The use of placebo in the control arm of a clinical trial is ethically acceptable when, as stated in the Declaration of Helsinki (Paragraph 29), "no proven prophylactic, diagnostic or therapeutic method exists." Usually, in this case, a placebo is scientifically preferable to no intervention. In certain circumstances, however, an alternative design may be both scientifically and ethically acceptable, and preferable; an example would be a clinical trial of a surgical intervention, because, for many surgical interventions, either it is not possible or it is ethically unacceptable to devise a suitable placebo; for another example, in certain vaccine trials an investigator might choose to provide for those in the 'control' arm a vaccine that is unrelated to the investigational vaccine.

Placebo-controlled trials that entail only minor risks. A placebo-controlled design may be ethically acceptable, and preferable on scientific grounds, when the condition for which patients/subjects are randomly assigned to placebo or active treatment is only a small deviation in physiological measurements, such as slightly raised blood pressure or a modest increase in serum cholesterol; and if delaying or omitting available treatment may cause only temporary discomfort (e.g., common headache) and no serious adverse consequences. The ethical review committee must be fully satisfied that the risks of withholding an established effective intervention are truly minor and short-lived.

Placebo control when active control would not yield reliable results. A related but distinct rationale for using a placebo control rather than an established effective intervention is that the documented experience with the established effective intervention is not sufficient to provide a scientifically reliable comparison with the intervention being investigated; it is then difficult, or even impossible, without using a placebo, to design a scientifically reliable study. This is not always, however, an ethically acceptable basis for depriving control subjects of an established effective intervention in clinical trials; only when doing so would not add any risk of serious harm, particularly irreversible harm, to the subjects would it be ethically acceptable to do so. In some cases, the condition at which the intervention is aimed (for example, cancer or HIV/AIDS) will be too serious to deprive control subjects of an established effective intervention.

This latter rationale *(when active control would not yield reliable results)* differs from the former *(trials that entail only minor risks)* in emphasis. In trials that entail only minor risks the investigative interventions are aimed at relatively trivial conditions, such as the common cold or hair loss; forgoing an established effective intervention for the duration

of a trial deprives control subjects of only minor benefits. It is for this reason that it is not unethical to use a placebo-control design. Even if it were possible to design a so-called "non-inferiority", or "equivalency", trial using an active control, it would still not be unethical in these circumstances to use a placebo-control design. In any event, the researcher must satisfy the ethical review committee that the safety and human rights of the subjects will be fully protected, that prospective subjects will be fully informed about alternative treatments, and that the purpose and design of the study are scientifically sound. The ethical acceptability of such placebo-controlled studies increases as the period of placebo use is decreased, and when the study design permits change to active treatment ("escape treatment") if intolerable symptoms occur.

Exceptional use of a comparator other than an established effective intervention. An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable. Accordingly, the proposed investigational intervention must be responsive to the health needs of the population from which the research subjects are recruited and there must be assurance that, if it proves to be safe and effective, it will be made reasonably available to that population. Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy.

However, some people strongly object to the exceptional use of a comparator other than an established effective intervention because it could result in exploitation of poor and disadvantaged populations. The objection rests on three arguments:

- Placebo control could expose research subjects to risk of serious or irreversible harm when the use of an established effective intervention as comparator could avoid the risk.

- Not all scientific experts agree about conditions under which an established effective intervention used as a comparator would not yield scientifically reliable results.

- An economic reason for the unavailability of an established effective intervention cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study.

Placebo control when an established effective intervention is not available in the host country. The question addressed here is: when should an exception be allowed to the

general rule that subjects in the control arm of a clinical trial should receive an established effective intervention?

The usual reason for proposing the exception is that, for economic or logistic reasons, an established effective intervention is not in general use or available in the country in which the study will be conducted, whereas the investigational intervention could be made available, given the finances and infrastructure of the country.

Another reason that may be advanced for proposing a placebo-controlled trial is that using an established effective intervention as the control would not produce scientifically reliable data relevant to the country in which the trial is to be conducted. Existing data about the effectiveness and safety of the established effective intervention may have been accumulated under circumstances unlike those of the population in which it is proposed to conduct the trial; this, it may be argued, could make their use in the trial unreliable. One reason could be that the disease or condition manifests itself differently in different populations, or other uncontrolled factors could invalidate the use of existing data for comparative purposes.

The use of placebo control in these circumstances is ethically controversial, for the following reasons:

- Sponsors of research might use poor countries or communities as testing grounds for research that would be difficult or impossible in countries where there is general access to an established effective intervention, and the investigational intervention, if proven safe and effective, is likely to be marketed in countries in which an established effective intervention is already available and it is not likely to be marketed in the host country.

- The research subjects, both active-arm and control-arm, are patients who may have a serious, possibly life-threatening, illness. They do not normally have access to an established effective intervention currently available to similar patients in many other countries. According to the requirements of a scientifically reliable trial, investigators, who may be their attending physicians, would be expected to enrol some of those patients/subjects in the placebo-control arm. This would appear to be a violation of the physician's fiduciary duty of undivided loyalty to the patient, particularly in cases in which known effective therapy could be made available to the patients.

An argument for exceptional use of placebo control may be that a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, seeks to develop an affordable intervention specifically for a health problem affecting its population. There may then be less reason for concern that a placebo design is exploitative, and therefore unethical, as the health authority has responsibility for the population's health, and there are valid health grounds for testing an apparently beneficial intervention. In such circumstances an ethical review committee may determine that the

proposed trial is ethically acceptable, provided that the rights and safety of subjects are safeguarded.

Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established effective intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country. This may be difficult to determine, however, as it is clear that, with sufficient persistence and ingenuity, ways may be found of accessing previously unattainable medicinal products, and thus avoiding the ethical issue raised by the use of placebo control.

When the rationale of proposing a placebo-controlled trial is that the use of an established effective intervention as the control would not yield scientifically reliable data relevant to the proposed host country, the ethical review committee in that country has the option of seeking expert opinion as to whether use of an established effective intervention in the control arm would invalidate the results of the research.

An "equivalency trial" as an alternative to a placebo-controlled trial. An alternative to a placebo-control design in these circumstances would be an "equivalency trial", which would compare an investigational intervention with an established effective intervention and produce scientifically reliable data. An equivalency trial in a country in which no established effective intervention is available is not designed to determine whether the investigational intervention is superior to an established effective intervention currently used somewhere in the world; its purpose is, rather, to determine whether the investigational intervention is, in effectiveness and safety, equivalent to, or almost equivalent to, the established effective intervention. It would be hazardous to conclude, however, that an intervention demonstrated to be equivalent, or almost equivalent, to an established effective intervention is better than nothing or superior to whatever intervention is available in the country; there may be substantial differences between the results of superficially identical clinical trials carried out in different countries. If there are such differences, it would be scientifically acceptable and ethically preferable to conduct such 'equivalency' trials in countries in which an established effective intervention is already available.

If there are substantial grounds for the ethical review committee to conclude that an established effective intervention will not become available and implementable, the committee should obtain assurances from the parties concerned that plans have been agreed for making the investigational intervention reasonably available in the host country or community once its effectiveness and safety have been established. Moreover, when the study has external sponsorship, approval should usually be dependent on the sponsors and the health authorities of the host country having engaged in a process of negotiation and planning, including justifying the study in regard to local health-care needs.

Means of minimizing harm to placebo-control subjects. Even when placebo controls are justified on one of the bases set forth in the guideline, there are means of minimizing the possibly harmful effect of being in the control arm.

First, a placebo-control group need not be untreated. An add-on design may be employed when the investigational therapy and a standard treatment have different mechanisms of action. The treatment to be tested and placebo are each added to a standard treatment. Such studies have a particular place when a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret [*International Conference on Harmonisation (ICH) Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000*]. In testing for improved treatment of life-threatening diseases such as cancer, HIV/AIDS, or heart failure, add-on designs are a particularly useful means of finding improvements in interventions that are not fully effective or may cause intolerable side-effects. They have a place also in respect of treatment for epilepsy, rheumatism and osteoporosis, for example, because withholding of established effective therapy could result in progressive disability, unacceptable discomfort or both.

Second, as indicated in Guideline 8 Commentary, when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator minimizes harmful effects of placebo-control studies by providing in the research protocol for the monitoring of research data by an independent Data and Safety Monitoring Board (DSMB). One function of such a board is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior therapy. The board fulfils the latter function by means of interim analyses of the data pertaining to efficacy to ensure that the trial does not continue beyond the point at which an investigational therapy is demonstrated to be effective. Normally, at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

In some cases the DSMB is called upon to perform "conditional power calculations", designed to determine the probability that a particular clinical trial could ever show that the investigational therapy is effective. If that probability is very small, the DSMB is expected to recommend termination of the clinical trial, because it would be unethical to continue it beyond that point.

In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study.

Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research

Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

Commentary on Guideline 12

General considerations: Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term; such benefits include the direct benefits of participation as well as the benefits of the new knowledge that the research is designed to yield. When burdens or benefits of research are to be apportioned unequally among individuals or groups of persons, the criteria for unequal distribution should be morally justifiable and not arbitrary. In other words, unequal allocation must not be inequitable. Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status or gender unless there is a sound scientific reason to do otherwise.

In the past, groups of persons were excluded from participation in research for what were then considered good reasons. As a consequence of such exclusions, information about the diagnosis, prevention and treatment of diseases in such groups of persons is limited. This has resulted in a serious class injustice. If information about the management of diseases is considered a benefit that is distributed within a society, it is unjust to deprive groups of persons of that benefit. Such documents as the Declaration of Helsinki and the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research,* and the policies of many national governments and professional societies, recognize the need to redress these injustices by encouraging the participation of previously excluded groups in basic and applied biomedical research.

Members of vulnerable groups also have the same entitlement to access to the benefits of investigational interventions that show promise of therapeutic benefit as persons not considered vulnerable, particularly when no superior or equivalent approaches to therapy are available.

There has been a perception, sometimes correct and sometimes incorrect, that certain groups of persons have been overused as research subjects. In some cases such overuse has been based on the administrative availability of the populations. Research hospitals are often located in places where members of the lowest socioeconomic classes reside, and this has resulted in an apparent overuse of such persons. Other groups that may have been overused because they were conveniently available to researchers include students in investigators' classes, residents of long-term care facilities and subordinate members of hierarchical institutions. Impoverished groups have been overused because of their willingness to serve as subjects in exchange for relatively small stipends. Prisoners have

been considered ideal subjects for Phase I drug studies because of their highly regimented lives and, in many cases, their conditions of economic deprivation.

Overuse of certain groups, such as the poor or the administratively available, is unjust for several reasons. It is unjust to selectively recruit impoverished people to serve as research subjects simply because they can be more easily induced to participate in exchange for small payments. In most cases, these people would be called upon to bear the burdens of research so that others who are better off could enjoy the benefits. However, although the burdens of research should not fall disproportionately on socio-economically disadvantaged groups, neither should such groups be categorically excluded from research protocols. It would not be unjust to selectively recruit poor people to serve as subjects in research designed to address problems that are prevalent in their group – malnutrition, for example. Similar considerations apply to institutionalized groups or those whose availability to the investigators is for other reasons administratively convenient.

Not only may certain groups within a society be inappropriately overused as research subjects, but also entire communities or societies may be overused. This has been particularly likely to occur in countries or communities with insufficiently well-developed systems for the protection of the rights and welfare of human research subjects. Such overuse is especially questionable when the populations or communities concerned bear the burdens of participation in research but are extremely unlikely ever to enjoy the benefits of new knowledge and products developed as a result of the research. (See Guideline 10: *Research in populations and communities with limited resources.)*

Guideline 13: Research involving vulnerable persons

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Commentary on Guideline 13

Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

General considerations. The central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of the burdens and benefits of research participation. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (Guidelines

14,15) and include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that:

- the research could not be carried out equally well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class– either the actual subjects or other similarly situated members of the vulnerable class;
- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;
- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and,
- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

Other vulnerable groups. The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse. Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police. Because they work in close proximity to investigators, they tend to be called upon more often than others to serve as research subjects, and this could result in inequitable distribution of the burdens and benefits of research.

Elderly persons are commonly regarded as vulnerable. With advancing age, people are increasingly likely to acquire attributes that define them as vulnerable. They may, for example, be institutionalized or develop varying degrees of dementia. If and when they acquire such vulnerability-defining attributes, and not before, it is appropriate to consider them vulnerable and to treat them accordingly.

Other groups or classes may also be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people and the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless persons, nomads, refugees or displaced persons, prisoners, patients with incurable disease, individuals who are politically powerless, and members of communities unfamiliar with modern medical concepts. To the extent that these and

other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be reviewed and applied, where relevant.

Persons who have serious, potentially disabling or life-threatening diseases are highly vulnerable. Physicians sometimes treat such patients with drugs or other therapies not yet licensed for general availability because studies designed to establish their safety and efficacy have not been completed. This is compatible with the Declaration of Helsinki, which states in Paragraph 32: *" In the treatment of a patient, where proven...therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new... therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering"*. Such treatment, commonly called 'compassionate use', is not properly regarded as research, but it can contribute to ongoing research into the safety and efficacy of the interventions used.

Although, on the whole, investigators must study less vulnerable groups before involving more vulnerable groups, some exceptions are justified. In general, children are not suitable for Phase I drug trials or for Phase I or II vaccine trials, but such trials may be permissible after studies in adults have shown some therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified when a vaccine has shown evidence of preventing or slowing progression of an infectious disease in adults, or Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children (Appendix 3: *The phases of clinical trials of vaccines and drugs*).

Guideline 14: Research involving children

Before undertaking research involving children, the investigator must ensure that:

- **the research might not equally well be carried out with adults;**
- **the purpose of the research is to obtain knowledge relevant to the health needs of children;**
- **a parent or legal representative of each child has given permission;**
- **the agreement (assent) of each child has been obtained to the extent of the child`s capabilities; and,**
- **a child`s refusal to participate or continue in the research will be respected.**

Commentary on Guideline 14

Justification of the involvement of children in biomedical research. The participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible (cf. vaccine trials), as well as for clinical trials of drugs that are designed for children as well as adults. In the past, many new products were not tested for children though they were directed towards diseases also occurring in childhood; thus children either did not benefit from these new drugs or were exposed to them though little was known about their specific effects or safety in children. Now it is widely agreed that, as a general rule, the sponsor of any new therapeutic, diagnostic or preventive product that is likely to be indicated for use in children is obliged to evaluate its safety and efficacy for children before it is released for general distribution.

Assent of the child. The willing cooperation of the child should be sought, after the child has been informed to the extent that the child's maturity and intelligence permit. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another; in some countries the "age of consent" established in their different provinces, states or other political subdivisions varies considerably. Often children who have not yet reached the legally established age of consent can understand the implications of informed consent and go through the necessary procedures; they can therefore knowingly agree to serve as research subjects. Such knowing agreement, sometimes referred to as assent, is insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative.

Some children who are too immature to be able to give knowing agreement, or assent, may be able to register a 'deliberate objection', an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child, for example, is to be distinguished from the behaviour of an infant, who is likely to cry or withdraw in response to almost any stimulus. Older children, who are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons related to age for involving younger children first.

A deliberate objection by a child to taking part in research should always be respected even if the parents have given permission, unless the child needs treatment that is not available outside the context of research, the investigational intervention shows promise of therapeutic benefit, and there is no acceptable alternative therapy. In such a case, particularly if the child is very young or immature, a parent or guardian may override the child`s objections. If the child is older and more nearly capable of independent informed consent, the investigator should seek the specific approval or clearance of the scientific and ethical review committees for initiating or continuing with the investigational treatment. If child subjects become capable of independent informed consent during the research, their informed consent to continued participation should be sought and their decision respected.

A child with a likely fatal illness may object or refuse assent to continuation of a burdensome or distressing intervention. In such circumstances parents may press an investigator to persist with an investigational intervention against the child`s wishes. The

investigator may agree to do so if the intervention shows promise of preserving or prolonging life and there is no acceptable alternative treatment. In such cases, the investigator should seek the specific approval or clearance of the ethical review committee before agreeing to override the wishes of the child.

Permission of a parent or guardian. The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures. It may be assumed that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission. Even when the law requires parental permission, however, the assent of the child must be obtained.

In some jurisdictions, some individuals who are below the general age of consent are regarded as "emancipated" or "mature" minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. They may be married or pregnant or be already parents or living independently. Some studies involve investigation of adolescents' beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. For studies on these topics, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the adolescents at some risk of questioning or even intimidation by their parents.

Because of the issues inherent in obtaining assent from children in institutions, such children should only exceptionally be subjects of research. In the case of institutionalized children without parents, or whose parents are not legally authorized to grant permission, the ethical review committee may require sponsors or investigators to provide it with the opinion of an independent, concerned, expert advocate for institutionalized children as to the propriety of undertaking the research with such children.

Observation of research by a parent or guardian. A parent or guardian who gives permission for a child to participate in research should be given the opportunity, to a reasonable extent, to observe the research as it proceeds, so as to be able to withdraw the child if the parent or guardian decides it is in the child's best interests to do so.

Psychological and medical support. Research involving children should be conducted in settings in which the child and the parent can obtain adequate medical and psychological support. As an additional protection for children, an investigator may, when possible, obtain the advice of a child's family physician, paediatrician or other health-care provider on matters concerning the child's participation in the research.

(See also Guideline 8: *Benefits and risks of study participation*; Guideline 9: *Special limitations on risks when subjects are not capable of giving consent*; and Guideline 13: *Research involving vulnerable persons.)*

Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- **such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;**
- **the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;**
- **the consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,**
- **in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.**

Commentary on Guideline 15

General considerations. Most individuals with mental or behavioural disorders are capable of giving informed consent; this Guideline is concerned only with those who are not capable or who because their condition deteriorates become temporarily incapable. They should never be subjects of research that might equally well be carried out on persons in full possession of their mental faculties, but they are clearly the only subjects suitable for a large part of research into the origins and treatment of certain severe mental or behavioural disorders.

Consent of the individual. The investigator must obtain the approval of an ethical review committee to include in research persons who by reason of mental or behavioural disorders are not capable of giving informed consent. The willing cooperation of such persons should be sought to the extent that their mental state permits, and any objection on their part to taking part in any study that has no components designed to benefit them directly should always be respected. The objection of such an individual to an investigational intervention intended to be of therapeutic benefit should be respected unless there is no reasonable medical alternative and local law permits overriding the objection. The agreement of an immediate family member or other person with a close personal relationship with the individual should be sought, but it should be recognized that these proxies may have their own interests that may call their permission into question. Some relatives may not be primarily concerned with protecting the rights and

welfare of the patients. Moreover, a close family member or friend may wish to take advantage of a research study in the hope that it will succeed in "curing" the condition. Some jurisdictions do not permit third-party permission for subjects lacking capacity to consent.Legal authorization may be necessary to involve in research an individual who has been committed to an institution by a court order.

Serious illness in persons who because of mental or behavioural disorders are unable to give adequately informed consent. Persons who because of mental or behavioural disorders are unable to give adequately informed consent and who have, or are at risk of, serious illnesses such as HIV infection, cancer or hepatitis should not be deprived of the possible benefits of investigational drugs, vaccines or devices that show promise of therapeutic or preventive benefit, particularly when no superior or equivalent therapy or prevention is available. Their entitlement to access to such therapy or prevention is justified ethically on the same grounds as is such entitlement for other vulnerable groups.

Persons who are unable to give adequately informed consent by reason of mental or behavioural disorders are, in general, not suitable for participation in formal clinical trials except those trials that are designed to be responsive to their particular health needs and can be carried out only with them.

(See also Guidelines 8: *Benefits and risks of study participation;* 9: *Special limitations on risks when subjects are not capable of giving consent;* and 13: *Research involving vulnerable persons*.)

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

Commentary on Guideline 16

Women in most societies have been discriminated against with regard to their involvement in research. Women who are biologically capable of becoming pregnant

have been customarily excluded from formal clinical trials of drugs, vaccines and medical devices owing to concern about undetermined risks to the fetus. Consequently, relatively little is known about the safety and efficacy of most drugs, vaccines or devices for such women, and this lack of knowledge can be dangerous.

A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the benefits of the new knowledge derived from the trials. Further, it is an affront to their right of self-determination. Nevertheless, although women of childbearing age should be given the opportunity to participate in research, they should be helped to understand that the research could include risks to the fetus if they become pregnant during the research.

Although this general presumption favours the inclusion of women in research, it must be acknowledged that in some parts of the world women are vulnerable to neglect or harm in research because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering. When women in such situations are potential subjects in research, investigators need to exercise special care in the informed consent process to ensure that they have adequate time and a proper environment in which to take decisions on the basis of clearly given information.

Individual consent of women: In research involving women of reproductive age, whether pregnant or non-pregnant, only the informed consent of the woman herself is required for her participation. In no case should the permission of a spouse or partner replace the requirement of individual informed consent. If women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable. A strict requirement of authorization of spouse or partner, however, violates the substantive principle of respect for persons.

A thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. For women who are not pregnant at the outset of a study but who might become pregnant while they are still subjects, the consent discussion should include information about the alternative of voluntarily withdrawing from the study and, where legally permissible, terminating the pregnancy. Also, if the pregnancy is not terminated, they should be guaranteed a medical follow-up.

Guideline 17: Pregnant women as research participants.

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and

benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.

Research in this population should be performed only if it is relevant

to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity .

Commentary on Guideline 17

The justification of research involving pregnant women is complicated by the fact that it may present risks and potential benefits to two beings – the woman and the fetus – as well as to the person the fetus is destined to become. Though the decision about acceptability of risk should be made by the mother as part of the informed consent process, it is desirable in research directed at the health of the fetus to obtain the father's opinion also, when possible. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the fetus should be made by the woman as part of the informed consent process.

Especially in communities or societies in which cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate, or not to participate, in research. Special safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus. Where fetal abnormality is not recognized as an indication for abortion, pregnant women should not be recruited for research in which there is a realistic basis for concern that fetal abnormality may occur as a consequence of participation as a subject in research.

Investigators should include in protocols on research on pregnant women a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

Guideline 18: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Commentary on Guideline 18

Confidentiality between investigator and subject. Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means. During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality.

Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Drug regulatory authorities have the right to inspect clinical-trial records, and a sponsor's clinical-compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects.

Participation in HIV/AIDS drug and vaccine trials may impose upon the research subjects significant associated risks of social discrimination or harm; such risks merit consideration equal to that given to adverse medical consequences of the drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, subjects in vaccine trials must be enabled to demonstrate that their HIV seropositivity is due to their having been vaccinated rather than to natural infection. This may be accomplished by providing them with documents attesting to their participation in vaccine trials, or by maintaining a confidential register of trial subjects, from which information can be made available to outside agencies at a subject's request.

Confidentiality between physician and patient. Patients have the right to expect that their physicians and other health-care professionals will hold all information about them in strict confidence and disclose it only to those who need, or have a legal right to, the information, such as other attending physicians, nurses, or other health-care workers who perform tasks related to the diagnosis and treatment of patients. A treating physician should not disclose any identifying information about patients to an investigator unless each patient has given consent to such disclosure and unless an ethical review committee has approved such disclosure.

Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiological studies often make use of such records. For such studies it is usually impracticable to obtain the informed consent of each identifiable patient; an ethical review committee may waive the requirement for informed consent when this is consistent with the requirements of applicable law and provided that there are secure safeguards of confidentiality. (See also Guideline 4 Commentary: *Waiver of the consent requirement.)* In institutions in which records may be used for research purposes without the informed consent of patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement

in patient-information brochures. For research limited to patients' medical records, access must be approved or cleared by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

Issues of confidentiality in genetic research. An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process.

When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject`s physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labelled.

Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects` consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects`consent; such plans should be clearly explained during the process of obtaining informed consent.

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Commentary on Guideline 19

Guideline 19 is concerned with two distinct but closely related entitlements. The first is the uncontroversial entitlement to free medical treatment and compensation for accidental injury inflicted by procedures or interventions performed exclusively to accomplish the purposes of research (non-therapeutic procedures). The second is the entitlement of dependants to material compensation for death or disability occurring as a direct result of study participation. Implementing a compensation system for research-related injuries or death is likely to be complex, however.

Equitable compensation and free medical treatment. Compensation is owed to research subjects who are disabled as a consequence of injury from procedures performed solely to accomplish the purposes of research. Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice. In the early stages of drug testing (Phase I and early Phase II), it is generally unreasonable to assume that an investigational drug holds out the prospect of direct benefit for the individual subject; accordingly, compensation is usually owed to individuals who become disabled as a result of serving as subjects in such studies.

The ethical review committee should determine in advance: i) the injuries for which subjects will receive free treatment and, in case of impairment, disability or handicap resulting from such injuries, be compensated; and ii) the injuries for which they will not be compensated. Prospective subjects should be informed of the committee's decisions, as part of the process of informed consent. As an ethical review committee cannot make such advance determination in respect of unexpected or unforeseen adverse reactions, such reactions must be presumed compensable and should be reported to the committee for prompt review as they occur.

Subjects must not be asked to waive their rights to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or compensation. The informed consent process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability or handicap. Prospective subjects should be informed that they will not need to take legal action to secure the free medical treatment or compensation for injury to which they may be entitled. They should also be told what medical service or organization or individual will provide the medical treatment and what organization will be responsible for providing compensation.

Obligation of the sponsor with regard to compensation. Before the research begins, the sponsor, whether a pharmaceutical company or other organization or institution, or a government (where government insurance is not precluded by law), should agree to provide compensation for any physical injury for which subjects are entitled to compensation, or come to an agreement with the investigator concerning the circumstances in which the investigator must rely on his or her own insurance coverage

(for example, for negligence or failure of the investigator to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses. Sponsors should seek adequate insurance against risks to cover compensation, independent of proof of fault.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.

Capacity-building may include, but is not limited to, the following activities:

- **establishing and strengthening independent and competent ethical review processes/ committees**
- **strengthening research capacity**
- **developing technologies appropriate to health-care and biomedical research**
- **training of research and health-care staff**
- **educating the community from which research subjects will be drawn**

Commentary on Guideline 20

External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research. Before undertaking research in a host country with little or no such capacity, external sponsors and investigators should include in the research protocol a plan that specifies the contribution they will make. The amount of capacity building reasonably expected should be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would entail relatively little, if any, such development, whereas a considerable contribution is to be expected of an external sponsor of, for instance, a large-scale vaccine field-trial expected to last two or three years.

The specific capacity-building objectives should be determined and achieved through dialogue and negotiation between external sponsors and host-country authorities. External sponsors would be expected to employ and, if necessary, train local individuals to function as investigators, research assistants or data managers, for example, and to provide, as necessary, reasonable amounts of financial, educational and other assistance for capacity-building. To avoid conflict of interest and safeguard the independence of review committees, financial assistance should not be provided directly to them; rather, funds should be made available to appropriate authorities in the host-country government or to the host research institution.

(See also Guideline 10: *Research in populations and communities with limited resources*)

Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

– health-care services that are essential to the safe conduct of the research;

– treatment for subjects who suffer injury as a consequence of research interventions; and,

– services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

Commentary on Guideline 21

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and document.

Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.

The obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation be provided for death or disability occurring as a consequence of such injury, is the subject of Guideline 19, on the scope and limits of such obligations.

When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care. In general, also, in the course of a study, sponsors should disclose to the proper health authorities information of public health concern arising from the research.

The obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10: *Research in populations and communities with limited resources.*

Appendix 1

Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.

(Include the items relevant to the study/project in question)

1. Title of the study;

2. A summary of the proposed research in lay/non-technical language.

3. A clear statement of the justification for the study, its significance in development and in meeting the needs of the country /population in which the research is carried out;

4. The investigators` views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them;

5. Summary of all previous studies on the topic, including unpublished studies known to the investigators and sponsors, and information on previously published research on the topic, including the nature, extent and relevance of animal studies and other preclinical and clinical studies;

6. A statement that the principles set out in these Guidelines will be implemented;

7. An account of previous submissions of the protocol for ethical review and their outcome;

8. A brief description of the site(s) where the research is to be conducted, including information about the adequacy of facilities for the safe and appropriate conduct of the research, and *relevant* demographic and epidemiological information about the country or region concerned;

9. Name and address of the sponsor;

10. Names, addresses, institutional affiliations, qualifications and experience of the principal investigator and other investigators;

11. The objectives of the trial or study, its hypotheses or research questions, its assumptions, and its variables;

12. A detailed description of the design of the trial or study. In the case of controlled clinical trials the description should include, but not be limited to, whether assignment to treatment groups will be randomized (including the method of randomization), and whether the study will be blinded (single blind, double blind), or open;

13. The number of research subjects needed to achieve the study objective, and how this was statistically determined;

14. The criteria for inclusion or exclusion of potential subjects, and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or for other reasons;

15. The justification for involving as research subjects any persons with limited capacity to consent or members of vulnerable social groups, and a description of special measures to minimize risks and discomfort to such subjects;

16. The process of recruitment, e.g., advertisements, and the steps to be taken to protect privacy and confidentiality during recruitment;

17. Description and explanation of all interventions (the method of treatment administration, including route of administration, dose, dose interval and treatment period for investigational and comparator products used);

18. Plans and justification for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to subjects;

19. Any other treatment that may be given or permitted, or contraindicated, during the study;

20. Clinical and laboratory tests and other tests that are to be carried out;

21. Samples of the standardized case-report forms to be used, the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of subjects with the treatment;

22. Rules or criteria according to which subjects may be removed from the study or clinical trial, or (in a multi-centre study) a centre may be discontinued, or the study may be terminated;

23. Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications;

24. The known or foreseen risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested;

25. For research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death;

26. Provision for continuing access of subjects to the investigational treatment after the study, indicating its modalities, the individual or organization responsible for paying for it, and for how long it will continue;

27. For research on pregnant women, a plan, if appropriate, for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

28. The potential benefits of the research to subjects and to others;

29. The expected benefits of the research to the population, including new knowledge that the study might generate;

30. The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent;

31. When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative;

32. An account of any economic or other inducements or incentives to prospective subjects to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the subjects, such as payment for medical services;

33. Plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect subjects' willingness to continue in the study;

34. Plans to inform subjects about the results of the study;

35. The provisions for protecting the confidentiality of personal data, and respecting the privacy of subjects, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject;

36. Information about how the code, if any, for the subjects' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency;

37. Any foreseen further uses of personal data or biological materials;

38. A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary;

39. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial and, if appropriate, the appointment for this purpose of an independent data-monitoring (data and safety monitoring) committee;

40. A list of the references cited in the protocol;

41. The source and amount of funding of the research: the organization that is sponsoring the research and a detailed account of the sponsor's financial

commitments to the research institution, the investigators, the research subjects, and, when relevant, the community;

42. The arrangements for dealing with financial or other conflicts of interest that might affect the judgement of investigators or other research personnel: informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the ethical review committee; and the transmission by that committee to the research subjects of the parts of the information that it decides should be passed on to them;

43. The time schedule for completion of the study;

44. For research that is to be carried out in a developing country or community, the contribution that the sponsor will make to capacity-building for scientific and ethical review and for biomedical research in the host country, and an assurance that the capacity-building objectives are in keeping with the values and expectations of the subjects and their communities;

45. Particularly in the case of an industrial sponsor, a contract stipulating who possesses the right to publish the results of the study, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft of the text reporting the results;

46. In the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority;

47. Circumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people;

48. A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor to take appropriate action against such unacceptable procedures.

Appendix 2

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

<www.wma.net>

Appendix 3

THE PHASES OF CLINICAL TRIALS OF VACCINES AND DRUGS

Vaccine development

Phase I refers to the first introduction of a candidate vaccine into a human population for initial determination of its safety and biological effects, including immunogenicity. This phase may include studies of dose and route of administration, and usually involves fewer than 100 volunteers.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is immunogenicity.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease, involving a larger number of volunteers in a multicentre adequately controlled study.

Drug development

Phase I refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness.

Phase II investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.

Phase III trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.

Phase IV trials are conducted after the national drug registration authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect, to establish the incidence of adverse reactions, or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the pre-marketing phases (such as children or the elderly) or to establish a new clinical indication for a drug.

Such research is to be distinguished from marketing research, sales promotion studies, and routine post-marketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees (see Guideline 2).



The ethics of research related to healthcare in developing countries

NUFFIELD COUNCIL ON BIOETHICS

Published by
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3JS

Telephone: **020 7681 9619**
Fax: **020 7637 1712**
Email: **bioethics@nuffieldbioethics.org**
Website: **http://www.nuffieldbioethics.org**

ISBN 0 9522701 9 6
April 2002

To order a printed copy, please contact the Nuffield Council or visit the website.

© Nuffield Council on Bioethics 2002

All rights reserved. Apart from fair dealing for the purpose of private study, research, criticism or review, no part of the publication may be produced, stored in a retrieval system or transmitted in any form, or by any means, without prior permission of the copyright owners.

Printed by — Latimer Trend Group
Estover Road
Plymouth PL6 7PY

Cover designed by — Geoffrey Wadsley

The ethics of research related to healthcare in developing countries

NUFFIELD COUNCIL ON BIOETHICS

Nuffield Council on Bioethics

Professor Sir Ian Kennedy (Chairman)

Professor Martin Bobrow CBE (Deputy Chairman)

Professor Tom Baldwin
Professor Sir Kenneth Calman KCB FRSE
The Rt Rev Richard Harries DD FKC FRSL
Professor Bob Hepple QC
Mrs Rebecca Howard
Professor John Ledingham
Professor Catherine Peckham CBE
Professor Martin Raff FRS
Mr Nick Ross
Professor Hebert Sewell
Professor Dame Marilyn Strathern FBA
Professor Albert Weale FBA
Dr Alan Williamson FRSE

Secretariat

Dr Sandy Thomas (Director)
Ms Susan Bull (Assistant Director)
Ms Tor Lezemore (Assistant Director)
Mrs Julia Fox
Ms Yvonne Melia
Ms Nicola Perrin
Ms Amanda Jones
Ms Maria Gonzalez-Nogal
Mrs Elaine Talaat-Abdalla

The terms of reference are as follows:

1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

The Nuffield Council on Bioethics is funded jointly by the Medical Research Council, the Nuffield Foundation and the Wellcome Trust

Preface

Any report which is concerned with the way in which research related to human health is conducted will be relevant to a wide range of audiences. This Report, the main objective of which is to consider externally-sponsored research as it affects those in developing countries, is particularly broad in its scope. The Working Party met for almost two years and was sustained by a passionate concern for people who take part in research studies in the developing world. This was coupled with the complementary wish to see research into disease and illness being undertaken to the highest standards for the benefit of future generations of patients and for the improvement of the health of populations.

Early on the context of the Working Party's deliberations was defined. Fulfilling the moral duties of justice and respect in the face of poverty, a lack of resources and the potential for exploitation, presents distinctive challenges to sponsors. We recognised that many of these concern broader issues of public health, of governance and of a lack of facilities, funding and expertise in some parts of the world. Much of this we could do nothing about, other than express our concerns. However we could, within our remit, strongly advocate that appropriate safeguards, based on the ethical principles we identified, be put in place to protect those who take part in research studies.

Research related to healthcare has been hotly debated in recent years, and has been the subject of several reports and investigations. Our contribution should thus be seen as part of that debate and one which focuses on externally-sponsored research conducted in developing countries. We have consulted widely and made a number of fact-finding visits across the world. The Working Party itself was multinational and we reminded ourselves on a regular basis that there were many different ways of considering an ethical issue. Cultural, social and religious differences were part of the context within which we worked. We have therefore considered the issues from the point of view of a population or of a research participant who is being studied in a particular context. We hope that this will ensure that the breadth of our thinking will assist in the recommendations being taken forward.

The recommendations are relevant to a wide range of organisations, agencies and national governments, as well as to research participants themselves. They concern issues of consent, standards of care, ethical review, and what should be done once the research is completed. We hope that they will be widely debated and taken up. We intend to review the response to the Report in 18 months' time.

I should like to thank the members of the group for their hard work and enthusiasm, we worked well as a team. I would particularly like to thank the Director of the Nuffield Council on Bioethics, Dr Sandy Thomas for all her input into the work of the group and for keeping us on the straight and narrow. To Julia Fox, Yvonne Melia and Tor Lezemore for all they contributed. Special thanks however must go to Susan Bull, whose tireless work and good humour helped us to get to the end of the Report with style and with a sense of achievement. It has been a privilege to chair the Working Party and I hope that the Report will stimulate the discussion and debate which the issues deserve.



Kenneth C Calman.

Acknowledgements

The Working Party wishes to thank the many organisations and individuals who have assisted its work, particularly those who attended fact-finding meetings or submitted consultation responses. It would also like to thank those who responded to the Working Party's requests for advice on specific areas of the Report. In addition the Working Party is very grateful to Dr Vichai Chokevivat, Dr Soledad Diaz, Professor Sir Colin Dollery, Dame Rennie Fritchie DBE, Professor Helen Lambert, Professor Adetokunbo Lucas, Professor Ruth Macklin, Dr Vasantha Muthuswamy and Baroness Onora O'Neill, who all reviewed an earlier version of the Report. Their comments, which contained both far-reaching and detailed criticisms to which we have sought to respond, were extremely helpful.

The ethics of research related to healthcare in developing countries

Table of Contents

Council membership and terms of reference iii

Preface v

Acknowledgements vi

Working Party membership xi

Working Party terms of reference xiii

Executive summary xv

Section 1 Introduction 1

Chapter 1 **Introduction** 3

The scope of the Report 5
Background 5
Consent 6
Standards of care 7
Review of the ethics of research 9
What happens once research is over? 9

Section 2 The context 11

Chapter 2 **Healthcare: the economic context** 13

Introduction 15
Variations in life expectancy between countries 15
Variation in resources available for healthcare between countries 17
The 10/90 disequilibrium: research expenditure and premature mortality 21
The scope of externally-sponsored research 22
Setting priorities for research 24
Pharmaceutical R&D in developing countries 28
Developing new interventions 30
The future 34

Chapter 3 **Social and cultural issues** 37

Introduction 39
Prevalence of alternative medical systems 39
Combining modern healthcare and traditional medicine 40
Concepts of illness, disease, misfortune and death 40
The doctor–patient relationship; the healer–client relationship 42
Informing prospective participants about research 43
Decisions about research 43

Contents

Chapter 4 **The ethical framework** 47
Introduction 49
The duty to alleviate suffering 50
Respect for persons 51
Sensitivity to cultural differences 51
The duty not to exploit the vulnerable 52
From principle to practice 53

Chapter 5 **The framework of guidance** 55
Introduction 57
The historical context 57
International guidance for the conduct of research 59
The Declaration of Helsinki 59
The CIOMS guidelines 62
Other international guidance 62
National guidance for the conduct of research 62
The enforcement of guidance 64
Training 65
The development of national guidance 66

Section 3 **The issues** 67

Chapter 6 **Consent** 69
Introduction 71
Information 71
Issues which may arise when informing participants about research 73
Understanding information 74
Complex and novel concepts 74
Voluntariness 75
The assent/involvement of the community 76
Refusing to participate in research 77
Inducements 78
Recording consent 80
Situations where consent forms are inappropriate 82

Chapter 7 **Standards of care** 85
Introduction 87
Existing guidance 87
Defining the best current method of treatment 88
The appropriate standard of care for control groups in clinical trials 89
Avoiding exploitation 90
Responsibilities of researchers and sponsors 90
Unsafe practices 91
The importance of the research context 92
Defining a non-universal standard of care 94
Deviations from the national standard 95
Research into preventive measures 96
Care for other conditions 97

Chapter 8 **Ethical review of research** 99
Introduction 101
Levels of assessment 102

Relevance to priorities in healthcare 102
Scientific review 102
Ethical review of research 103
Requirements for effective ethical review of research 103
Meeting the costs of research ethics committees 106
Reviewing research in the sponsoring country and the country in which the research is conducted 107
Developing capacity for reviewing the ethics of research 108

Chapter 9 What happens once research over? 111
Introduction 113
The continuation of improvements in healthcare 115
Adverse effects 116
Compensation 116
Long-term surveillance 117
Provision of an intervention once the study is over 118
Providing interventions to the members of control groups 119
Providing interventions to all the participants in a research project once the study is over 120
Providing interventions to the wider community and beyond 121
The role of researchers 122
The role of sponsors, international agencies, governments and other bodies 123
The development of expertise in research 125

Section 4 Conclusions and recommendations 127

Chapter 10 Conclusions and recommendations 129
Introduction 131
Healthcare economics 132
Setting priorities for research 132
Social and cultural issues 133
Ethical principles 133
The framework of guidance 134
Consent 135
Standards of care 137
Ethical review of research 140
What happens once research is over? 141
Concluding comments: a framework for future action 143

Appendix 1 Guidance on research related to healthcare 145
Appendix 2 Types of research design 161
Appendix 3 Issues to be considered when reviewing research proposals 165
Appendix 4 Fact-finding meetings 171
Appendix 5 Method of working and consultation 175
Glossary and acronyms 183
Index 199

The ethics of research related to healthcare in developing countries

Members of the Working Party

Professor Sir Kenneth Calman (Chairman) is Vice-Chancellor and Warden, University of Durham

Dr Fred Binka is Associate Professor of Epidemiology, School of Public Health, University of Ghana

Professor Michael Elves is a former Director, Office of Scientific and Educational Affairs, Glaxo Wellcome plc

Professor V I Mathan is a senior Consultant for Health Research, Indian Council of Medical Research, National Institute of Epidemiology, Chennai, India

Professor Keith McAdam is Director, MRC Laboratories, Fajara, The Gambia

Dr Anne McLaren is at the Wellcome/CRC Institute, Cambridge

Professor Bhikhu Parekh is Centennial Professor, The Centre for the Study of Global Governance, London School of Economics

Professor David Parkin is Professor of Social Anthropology, All Souls College, Oxford

Professor Catherine Peckham CBE is Professor of Epidemiology, Institute of Child Health, University College London

Professor Povl Riis is at the Copenhagan Ministry of Science

Professor Nelson Sewankambo is Dean, Faculty of Medicine, Makerere University, Kampala, Uganda

Mrs Shahwar Sadeque is an educational & ICT Consultant

Professor Peter Smith is Head of the Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine

Dr Fabio Zicker is Coordinator, Research Capacity Strengthening, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

The ethics of research related to healthcare in developing countries

Terms of reference

1. To review the importance of healthcare-related research in humans, supported by those in more affluent countries and conducted, at least partly, in developing countries.
2. To identify and consider the ethical and social implications of conducting such research including:
   (a) who benefits from the research;
   (b) consent;
   (c) differences in cultural values;
   (d) differences in levels of healthcare between countries;
   (e) compatibility of ethical guidelines produced by international bodies;
   (f) the respective responsibilities of local and non-local ethics review bodies, and mechanisms for review and monitoring;
   (g) follow-up, including the possible implementation of findings, after the completion of research.
3. To make recommendations.

Executive summary

The purpose of this Report is to examine the ethical issues raised when research related to healthcare is carried out in developing countries and funded by sponsors from developed countries. Developing countries urgently need research to help to address the enormous burden of disease that they carry. The inequalities in resources between developed and developing countries pose a real risk of exploitation in the context of externally-sponsored research. Recognising that external sponsors differ in their motives for conducting research in developing countries, the Working Party considers that all countries should set national priorities related to their provision of healthcare. When externally-sponsored research is proposed which falls outside the national priorities, its relevance must be justified to the appropriate research ethics committees. To enhance the ability of developing countries to conduct research that is relevant to their needs, **the Working Party recommends that the development of local expertise in the provision of healthcare and in healthcare research should be an integral component of any proposed research.**

The Working Party recognises that those involved in externally-sponsored research are often faced with diverse and sometimes conflicting guidance as to what may be ethically acceptable. This Report aims to present an ethical framework for others to use when applying such guidance and to assist those involved in the development of national guidance for the ethical review of research. The ethical framework proposed in this Report is based on four principles: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences; and the duty not to exploit the vulnerable. It is crucial that these duties are respected when research is planned and conducted. The Working Party emphasises the critical importance of taking into account the context, social, cultural and economic, when applying these principles. Further, it identifies certain minimum requirements that must be met.

Consent

The Working Party concludes that in some cultural contexts it may be appropriate to obtain agreement from the particular community or assent from a senior family member, before any prospective participant in research is approached. However, genuine consent to participate in research must also always be obtained from each participant.

Standards of care

The Working Party concludes that the appropriate standard of care to be provided to members of a control group in a research project can only be defined in consultation with those who work within the country in which the research is to be conducted. It must then be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care[1] for the disease being studied. Where it is inappropriate to offer such a standard, the minimum that should be offered is the best intervention currently available as part of the national public health system.

1 We use the term 'universal standard of care' to indicate the best current method of treatment available anywhere in the world for a particular disease or condition.

Once a research project is completed

The Working Party concludes that it is unacceptable for research to begin without a decision having been made about whether or not participants in the control group will be offered an intervention shown to be successful on completion of the trial. Researchers should endeavour to secure post-trial access to effective interventions for all the participants in a trial who could benefit. In addition, the possibility of introducing and maintaining a successful treatment in the wider community should be considered before research is conducted. If it is thought that this will not be possible, researchers must justify to the relevant research ethics committee why the research should be carried out.

Reviewing the ethics of a research project

An effective system of review of the ethical propriety of research is a crucial safeguard for participants in research. It may, however, be absent or ineffective in some developing countries. **The Working Party recommends that all countries should establish an effective system for the ethical review of research, which includes the establishment and maintenance of research ethics committees that are independent of government and sponsors of research**. Research should be subject to ethical review in both the country(ies) hosting and the country(ies) sponsoring the research. The Working Party welcomes international initiatives for establishing research ethics committees, training their members and monitoring their development. Funding should be provided for these purposes by those who sponsor research in developing countries. **Furthermore, the Working Party recommends that national and international sponsors of research should ensure that adequate provision is made for training of all those professionals involved in research related to healthcare in the ethics of research.**

Section 1

Introduction

Chapter 1

Introduction

The scope of the Report

1.1 The purpose of this Report is to examine the ethical issues raised when research involving human participants, particularly clinical research, carried out in a developing country[1] is funded or undertaken by agencies or researchers from outside that country. This Report sets out the context in which discussions and decisions about research on healthcare in developing countries take place. It highlights the health problems that are faced on a global scale, the issues which arise when setting national priorities for research related to healthcare and the social and cultural contexts in which research is conducted. The Report sets out a framework for considering the ethical issues raised by externally-sponsored research related to healthcare in developing countries and provides an outline of the current guidelines governing the conduct of such research. It then focuses on the ethical issues which arise in four primary areas: standards of care; consent; review of the ethics of research; and what happens once research is over. In considering these issues solely in the context of research which is externally funded, we do not suggest that the ethical principles which apply to internally-funded, national research are in any way different.

1.2 The Working Party was conscious that many of the questions raised in this Report were intimately related to more general issues about economic disparities, injustice, deprivation, and exploitation. Although these broader issues are not addressed in depth, their impact on research related to healthcare and health provision is considered throughout. The Report does not set out guidelines for the conduct of research, but analyses the ethical issues involved in the current debates and recommends ways forward. We hope the Report will make a significant contribution to international debate on these topics and will be of use to those with an interest in this area, including researchers, sponsors and policymakers who will be involved directly or indirectly in research related to healthcare.

Background

1.3 Health has many determinants. These include social, cultural, economic, and environmental factors, genetic variation, and the quality of healthcare available. Research into these factors is an essential component of improving health and healthcare in developing and developed countries alike. Basic research into causes of diseases and possible treatments is also vital. The improvement of health worldwide therefore requires a continuing commitment to learn from the results of carefully designed and managed research studies involving individual participants and populations.

1.4 In the developing world, research to find new or improved medicines and vaccines is often given high priority. In many circumstances this is appropriate, but research to find better ways of delivering existing products and services to those in need is often equally or more important. Furthermore, 'non-medical' research such as that into provision of improved sanitation, clean water, better nutrition and personal preventive measures may impact on many diseases. The control of HIV infection requires not only research on treatments and potential vaccines, but also studies of behaviour. Thus a spectrum of research may benefit developing countries, ranging from research into genetic determinants of health and disease at one end to pragmatic means of implementing effective treatments at the other.

1 The Working Party debated at length the appropriate terminology to use to distinguish between countries at different levels of economic development, conscious that any classification of countries as 'developed' or 'developing' would be subject to dispute, and to change. It was decided to use the terms 'developed' and 'developing'. While these terms have limitations, they also have a certain currency and are generally understood.

1.5 Eighty percent of the world's population lives in developing countries, where both healthcare and research related to healthcare are severely constrained by limited financial and human resources, and by the lack of appropriate infrastructure to deliver healthcare. The imbalance between the need for means of prevention and treatment of disease and the ability to meet these needs is widely recognised. Research related to healthcare carried out in developing countries, often sponsored by developed countries, has made many outstanding contributions to the understanding, prevention and treatment of disease. This is not a recent phenomenon: research on diseases such as malaria, yellow fever and sleeping sickness has been carried out in what are now regarded as developing countries for more than a century.

1.6 An increasing amount of research related to healthcare is being supported in developing countries by governments, government agencies and voluntary organisations in developed countries, in addition to international bodies such as the World Health Organization (WHO) and multinational pharmaceutical companies. While some forms of sponsorship have been altruistic, others have been driven by academic interests which may not reflect national priorities for research in the country in which the research is to be conducted (see Box 2.6) or by economic considerations related to the marketing of healthcare products.

1.7 Wherever research is conducted, not only should the quality of the research be the same, but the value and respect given to participants in research should be equal. In developing countries the social, cultural and economic contexts in which research is conducted often differ from those in developed countries. Although there is broad agreement about the general ethical principles which apply to research related to healthcare, namely the duty to alleviate suffering, respect for persons, sensitivity to cultural differences and the duty not to exploit the vulnerable, there has been wide debate about the application of these principles in different research settings. Although the various international guidelines on research related to healthcare have provided some broadly based guidance, they have proved to be somewhat difficult to reconcile and apply in practice.

1.8 These difficulties were highlighted by the international controversy about a series of clinical trials into the prevention of mother-to-child transmission of HIV in 1997 (see Box 1.2). A deeper ethical analysis is therefore required not only to resolve inconsistencies in the guidance but to contribute to an improvement in practice. The most controversial aspects of research relating to healthcare in developing countries concern the process of consent to participate, the 'standard of care'[2] which is provided to participants in research and what happens once the research is over.

Consent

1.9 If research on healthcare is to be ethically acceptable, participants should be given the relevant information in a comprehensible manner, and must freely consent to take part. This is particularly important in developing countries where many participants consent to research because they believe it is their only means of receiving healthcare or other benefits. The procedures for consent that are used in developed countries may be ineffective or inappropriate in some developing countries because of differences in social and cultural environments. For example, participants in research may feel much more able to discuss research and ask questions within a meeting of the local community than on a one-to-one basis with researchers. In some regions, individuals may feel unable to refuse to participate in research that their elders, family members or community have assented to.

2 We are using the term 'standard of care' to mean the nature of the care and treatment that will be provided to participants in research.

1.10 The securing of genuine consent may also be complicated when communities in which research is to be conducted lack familiarity with the basic concept of medical research. Particular difficulties may arise when consent needs to be recorded in illiterate populations. The application of safeguards to protect such participants from possible exploitation is illustrated by the trial of vaccines for leprosy in Box 1.1. In some regions, participants may be unwilling to sign consent forms in the belief that they are signing away rights, or that other adverse repercussions may follow, such as stigmatisation following a positive HIV test (Box 1.1).

Standards of care

1.11 Much recent controversy has focused on the level of care provided to the control group in clinical trials. Should the control group receive the best current treatment available anywhere in the world, or treatment based on an alternative standard of care which takes local circumstances into account, such as the best treatment currently available in the country in which the research is being conducted? Where the best current treatment is inexpensive and simple to deliver, the answer is clear. However, in many circumstances the best current treatment available anywhere in the world may be very difficult to provide in developing countries. International attention was focused on this issue in 1997 when US-sponsored research into means of preventing mother-to-child transmission of HIV in Thailand was criticised as being unethical. The research used a locally-relevant standard of care (the control group received a placebo[3]) which would not have been acceptable if the research had been conducted in the US (see Box 1.2).

BOX 1.1 Towards an appropriate consent process: research into leprosy in Venezuela

In one study of a vaccine against leprosy carried out in rural Venezuela, researchers and prospective participants had no previous experience of an informed consent procedure. A process was designed in which the principal researcher visited communities where the research was to be conducted and explained it to community leaders. Following the approval of the community leaders, the research was explained to the community, followed by a question and answer session.

One to two months later members of the Ministry of Health visited the communities and asked individual participants if they understood what the research was about and whether or not they wished to participate. As many participants were not literate, their decision was recorded by a government worker, or in the presence of such a worker, without any of the researchers being present. Individual decisions were recorded and each participant either signed a form or gave a fingerprint.[1]

Written consent and confidentiality: HIV research in the Ivory Coast

A recent research programme which investigated possible methods of reducing mother-to-child transmission of HIV in the Ivory Coast, experienced low participation rates because of the requirement for HIV testing of pregnant women. This reluctance to be tested was due in part to the fear of social exclusion should relatives and, in particular, a husband or partner, become aware of a positive test result. The requirement for written consent to allow the HIV tests to be carried out led to considerable concern about breaches of confidentiality and subsequently, low participation rates.[2]

1 Bloom B (2001) Personal communication, Harvard School of Public Health and Convit J, Sampson C, Zuniga M, Smith PG, Plata J, Silva J *et al* (1992) Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results, **The Lancet**, 339(8791) 446–50.

2 Coulibaly D, Msellati P, Dedy S, Welffens-Ekra C and Dabis F (1998) Attitudes and behavior of pregnant women towards HIV screening in Abidjan (Ivory Coast) in 1995 and 1996, **Santé**, 8(3) 234–8.

3 A placebo is a treatment known to be without effect, usually used as a control to be compared against a potentially effective substance or method which is being subjected to clinical trial.

BOX 1.2 Standards of care

Research to prevent perinatal transmission of HIV in 1997

In September 1997, a paper by Lurie and Wolfe[1] and an editorial by Angell in the New England Journal of Medicine,[2] and an editorial in The Lancet[3] criticised placebo-controlled trials of short-course zidovudine given to HIV-infected pregnant women to prevent mother-to-child HIV transmission. The trials, some of which were conducted under the aegis of the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO, Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), were designed to determine whether relatively affordable and more feasible shorter courses of zidovudine given to pregnant women in developing countries would reduce the risk of mother-to-child transmission. They were conducted in countries where conventional local pregnancy care did not include antiretroviral treatment. The trial designs had been approved by ethics committees in the countries in which the trials were conducted.

Longer, more expensive and complex courses of zidovudine had been shown to reduce mother-to-child transmission rates in a trial conducted in the US and France.[4] Research in which the control group would be provided with a placebo would be deemed unethical in developed countries where antiretroviral treatment is available, following demonstration of the effectiveness of long-course zidovudine. The critics of the trials of a short course of treatment argued that it was unethical to give the control group a placebo when it has already been demonstrated that the longer courses reduced transmission of the virus.

Cerebro-spinal meningitis: standard of care in vaccine trials

Cerebro-spinal meningitis (CSM) occurs in epidemic form in parts of West Africa, causing thousands of deaths in epidemic years. One approach to controlling the disease is to develop an effective vaccine. Such a vaccine would need to be tested to determine whether it was effective and possible to deliver in those parts of West Africa with epidemic CSM.

In Africa, in epidemics of CSM, hundreds or thousands of people with signs of meningitis need to be diagnosed by lumbar puncture and treated by injections or antibiotics. One dose of treatment[5] may then be sufficient and the epidemic may be managed in an open area or school building. In contrast, in developed countries a case of CSM might be admitted to an intensive care facility.

Some might argue that for a trial of a CSM vaccine in a developing country, those in the trial should be provided with the best available treatment if they contract the disease, including admission to an intensive care facility where necessary. However, it would not only be very costly but also probably impractical to make such care available. If it is unethical to conduct research into a vaccine for CSM without a 'universal' standard of care being available, it is unclear where, in Africa, such research could be conducted.

1 Lurie P, Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, **New England Journal of Medicine**, 337(12): 853–6.
2 Angell M (1997) The ethics of clinical research in the third world, **New England Journal of Medicine**, 337(12): 847–9.
3 Editorial (1997) The ethics industry, **The Lancet**, 350: 897.
4 Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ *et al* (1994) Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Paediatric AIDS clinical trials group protocol 076 study group, **New England Journal of Medicine**, 331(18): 1173–80.
5 Such as oil-based chloramphenicol.

1.12 Other issues we address in the Report are the standard of care that should be provided to participants in a trial of a preventive intervention, such as a vaccine, who become infected with the disease against which the vaccine was designed to protect. We also consider the responsibility researchers have for those participants who become ill during the research with a disease which is unrelated to the disease being studied.

Review of the ethics of research

1.13 Effective review of the ethics of scientific and medical research is essential to ensure that unethical research is not permitted. Notwithstanding that the integrity of the researcher is of critical importance, the accepted method of ensuring that unethical research is prevented is through the establishment of a system in which research ethics committees undertake independent review of scientific protocols. In developed countries and a number of developing countries, such review is a prerequisite for research involving human participants. However, properly functioning research ethics committees are often absent or under-resourced in developing countries. In addition there may not be a pool of sufficiently trained and independent personnel to serve on a committee, and committees may not have the resources required to cover their administrative costs.

What happens once research is over?

1.14 Not all research projects will have results that can be translated directly into practice: research into the natural history of a disease, or the progression of an illness, may not have any immediate practical application. Trials of a medicine may reveal that it is not as effective as expected, or is unsafe, and therefore unsuitable for general use. However, research related to healthcare is usually designed to obtain results that will lead to an improvement in the prevention, diagnosis, treatment, or cure of a disease. One issue that arises when considering whether it is appropriate to conduct a specific research study within a developing country is whether the intervention being studied is likely to be affordable in that country if it is shown to be effective. This will often not be a straightforward issue: as noted in Box 1.3, expensive interventions that may appear too costly to implement in a poor country may become affordable within a short period of time while relatively affordable interventions may still be difficult to implement. Furthermore, interventions involving expensive equipment (such as magnetic resonance imaging (MRI) scanners), highly trained personnel (such as surgeons) or large numbers of trained staff (as in some counselling programmes for sexually transmitted diseases (STDs)) are unlikely to undergo such rapid and substantial reductions in cost.[4]

1.15 Issues we discuss in the Report include whether it is acceptable to conduct research if the benefits of that research will not be made available to the community in

BOX 1.3 After research is over: hepatitis B vaccination

At the time of a large-scale trial of a hepatitis B vaccine conducted in The Gambia (performed with vaccine donated by the manufacturer), the market price of vaccine was about US $60 per course (or US $20 per dose). However, within a few years the market price for developing countries had dropped to approximately US $1–2 per course bringing it much closer to the price that many such countries could afford.

Hepatitis B vaccine has since been introduced successfully on a national basis in The Gambia and Taiwan and has been demonstrated to induce strong and long-lasting protection against the hepatitis B carrier state (the major precursor of liver cancer). These developments have provided a very strong stimulus to find cheaper ways of producing the vaccine and for the introduction of this vaccine into the childhood immunisation programmes of many developing countries.

4 A recent commentary in **The Lancet** noted that social programmes such as HIV Voluntary Counselling and Testing (VCT) had been given low priority in developing countries because of their high requirements (particularly in cost-terms) on logistics and skills. However, research in the same edition of the journal found such programmes to be comparable in cost to a number of existing interventions for HIV. See Van de Perre P (2000) HIV voluntary counselling and testing in community health services, **The Lancet**, 356(9224) 86–7.

which the research was undertaken. We also consider where the responsibility for making a successful intervention generally available belongs and what role, if any, the researchers and sponsor have. In the case of participants in research who have chronic diseases such as HIV/AIDS, we address who has responsibility for providing continuing care after the research study is completed and what the standard of care should be.

Section 2

The context

Chapter 2

Healthcare: the economic context

Introduction

2.1 The great disparities between levels of health across the world correlate in general quite closely with the degree of socio-economic development of different countries. Not surprisingly, people living in poorer countries tend to have significantly higher rates of morbidity[1] and mortality than those living in wealthier countries. Historically, in the developed world, improved levels of health have been closely correlated with social and economic development.[2] In the more recent past, the same has held true in countries that are still classed as developing, and this relationship is likely to continue to hold in the future. However, certain countries or regions, such as Sri Lanka, Cuba and some states in India, have achieved improvements in health disproportionate to the development of their economy. This is usually because of the healthcare and educational systems adopted as a result of specific government policies.

2.2 Research into the diseases affecting developing countries has to be seen within the context of their socio-economic conditions. Many would regard the wide disparities in wealth between countries, and often between different groups within countries, as inherently unethical and consider that redressing these imbalances should be given a high priority. It is highly likely that a more equitable distribution of resources (wealth) would lead to much greater equality in the health status of different populations. However, some medical or health-related interventions that will improve health status, including vaccines against important infectious diseases such as AIDS, TB and malaria, could be deployed in advance of economic development, and may even promote such development.

2.3 However, it would be inappropriate to introduce or promote new interventions in developing countries without prior research into the risks and benefits for the populations in those countries. Even interventions that have been shown to be effective in specific populations will need to be carefully evaluated before being introduced into other areas where the local environmental, ecological and genetic profiles are very different. This kind of research in healthcare is an important priority for developing countries to assist in the proper selection and use of disease-reducing interventions and often needs to be conducted in the country where use of the intervention is proposed. Such research is often expensive and one form of assistance that several developed countries give to developing countries is the funding and provision of scientific and technical support to help promote and foster the conduct of appropriate research.

2.4 In this chapter we first review the disparities in the levels of health between countries and then describe the variation in the resources they have available for healthcare and promotion. Against this background we then discuss the measures involved in developing interventions for preventing or treating disease.

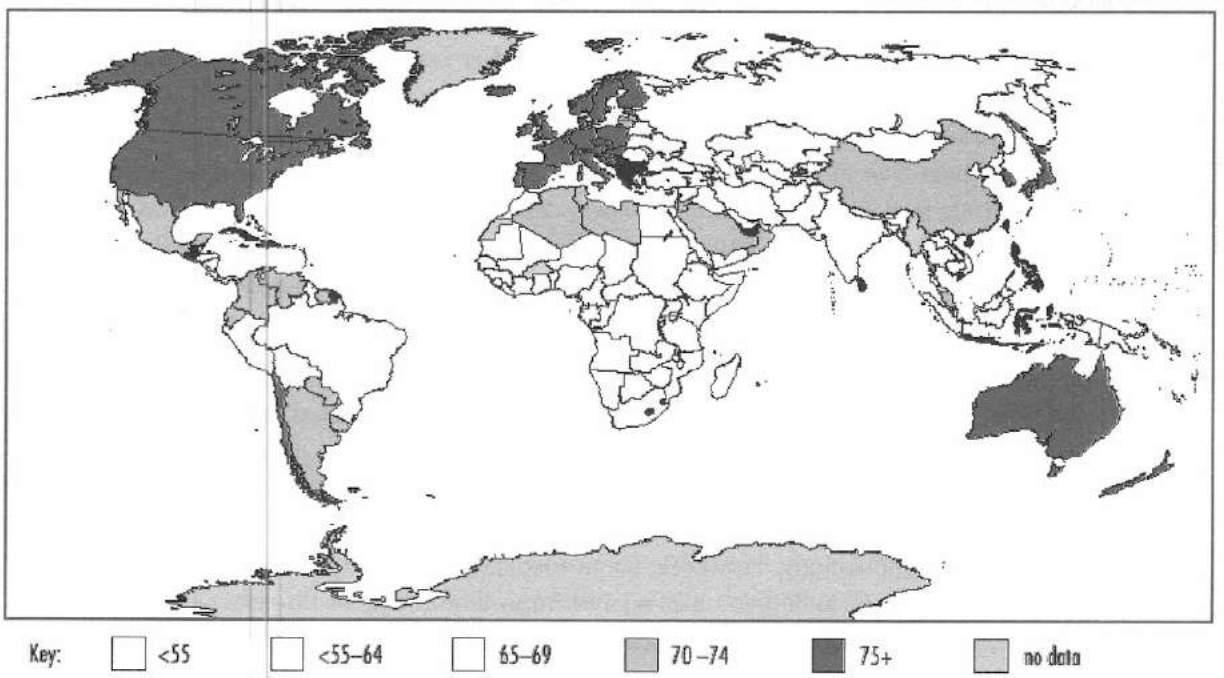
Variations in life expectancy between countries

2.5 The wide disparity in levels of morbidity and mortality between countries can be illustrated by examining the variation in life expectancy at birth. Figure 2.1 is a world map showing the average number of years that a live-born baby might expect to live in different countries.[3] Most of those born in the developed world can expect to live in excess of 70 years, whereas in the majority of African countries average life expectancy is less than 55 years, while in others it is less than 40 years (for example Zambia 38.5; Malawi 37.8 and Sierra Leone 34.3).[4]

1 Levels of sickness and ill health.
2 See for example, McKeown T (1976) **The Role of Medicine: Dream, Mirage or Nemesis**, Nuffield Provincial Hospitals Trust, London.
3 Based on estimated age-specific mortality rates in 1997.
4 World Health Organization (2000) **The World Health Report 2000. Health Systems: Improving Performance**, WHO, Geneva.

Figure 2.1:

Global map of expectation of life at birth



Redrawn from the World Bank Group's web site at: http://knowledge.worldbank.org/scripts/esrimpa.dll?name=gisonline&cmd=start map&view=21. (areas that were unclear on the original are shown in black)

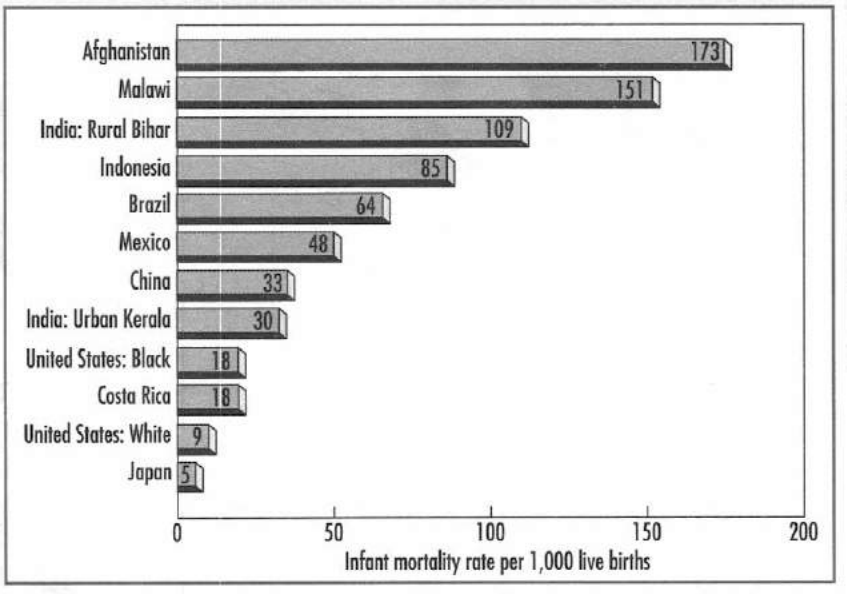
2.6 In an attempt to include morbidity as well as mortality in a summary measure of health, the World Health Organization (WHO) has calculated the average 'disability-adjusted life expectancy' for 191 countries.[5] This is most easily understood as the expectation of the total life lived in full health. Thus, it takes account of years lived with sickness and disease by discounting some of that time according to the seriousness of such conditions. The differences between countries based on disability-adjusted life expectancy are even greater than those based on simple expectation of life at birth. The estimates range from 74.5 years for Japan to 25.9 years for Sierra Leone. The majority of developed countries have estimates in excess of 70 years[6] while many African countries have estimates below 40 years.[7] Life expectancies in eastern and central Africa are particularly low because of the devastating effects of the current AIDS epidemic. In general, the levels of health in Asia and Latin America are intermediate between, on the one hand, Japan, North America and Western Europe and, on the other hand, Africa. However, the variation between different countries in each of these regions is substantial. [8]

2.7 An important reason for the differences in life expectancy is the variation in mortality rates among infants and young children. The scale of these differences is illustrated by infant mortality rates[9] in a selection of different countries (Figure 2.2). These range from 5/1000 for Japan to 173/1000 in Afghanistan.[10] There are also substantial variations within countries, as for example between the states of Bihar and Kerala in India and between African-Americans and

5 World Health Organization (2000) **The World Health Report 2000. Health Systems: Improving Performance**, WHO, Geneva.
6 For example France 73.1, UK 71.7, US 70 years
7 For example Kenya 39.4, Tanzania 36.0, Zimbabwe 32.9, Uganda 32.7, Zambia 30.3, Malawi 29.4 years.
8 For example, in Latin America disability-adjusted life expectancies range from 68.6 years in Chile, 68.4 in Cuba and 59.1 in Brazil to 53.3 in Bolivia. In Asia, it ranges from 69.3 years in Singapore and 62.8 in Sri Lanka through to 49.5 in Nepal and 37.7 in Afghanistan.
9 The number of children dying in the first year of life, per 1000 children born.
10 Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.

Figure 2.2:

Infant mortality rate in selected populations



Reproduced with permission from Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, OUP, New York.

whites in the US. Similar variability between countries is evident with respect to child mortality rates, as illustrated in Figure 2.3.[11]

2.8 Much of the difference between mortality rates in developed and developing countries is due to communicable diseases such as AIDS, tuberculosis, malaria, respiratory infections and diarrhoeal diseases. Figure 2.4 shows the disability-adjusted life years (DALYs) lost in three different regions of the world due to communicable diseases, non-communicable diseases and injuries.[12] Nearly three-quarters of the lost DALYs are attributable to communicable diseases in sub-Saharan Africa, compared to only about 10% of lost DALYs in many developed countries.

2.9 Until recently, when the effects of the AIDS epidemic began to be reflected in rising rates of mortality, life expectancies had been rising in most countries. They have continued to do so except, generally, in those countries worst hit by the AIDS epidemic, or those in which there has been war. The improvements in life expectancy are likely to be due to improved standards of living and important advances in the development of interventions to prevent or treat disease. The expanded programme of immunisation has been perhaps the most important contributor to lowering infant and child mortality rates. This has raised vaccination rates against some preventable diseases, such as polio and measles, to high levels in many countries. However, for many diseases that cause significant numbers of deaths during childhood, such as malaria, diarrhoeal diseases and respiratory infections, effective vaccines have not yet been developed.

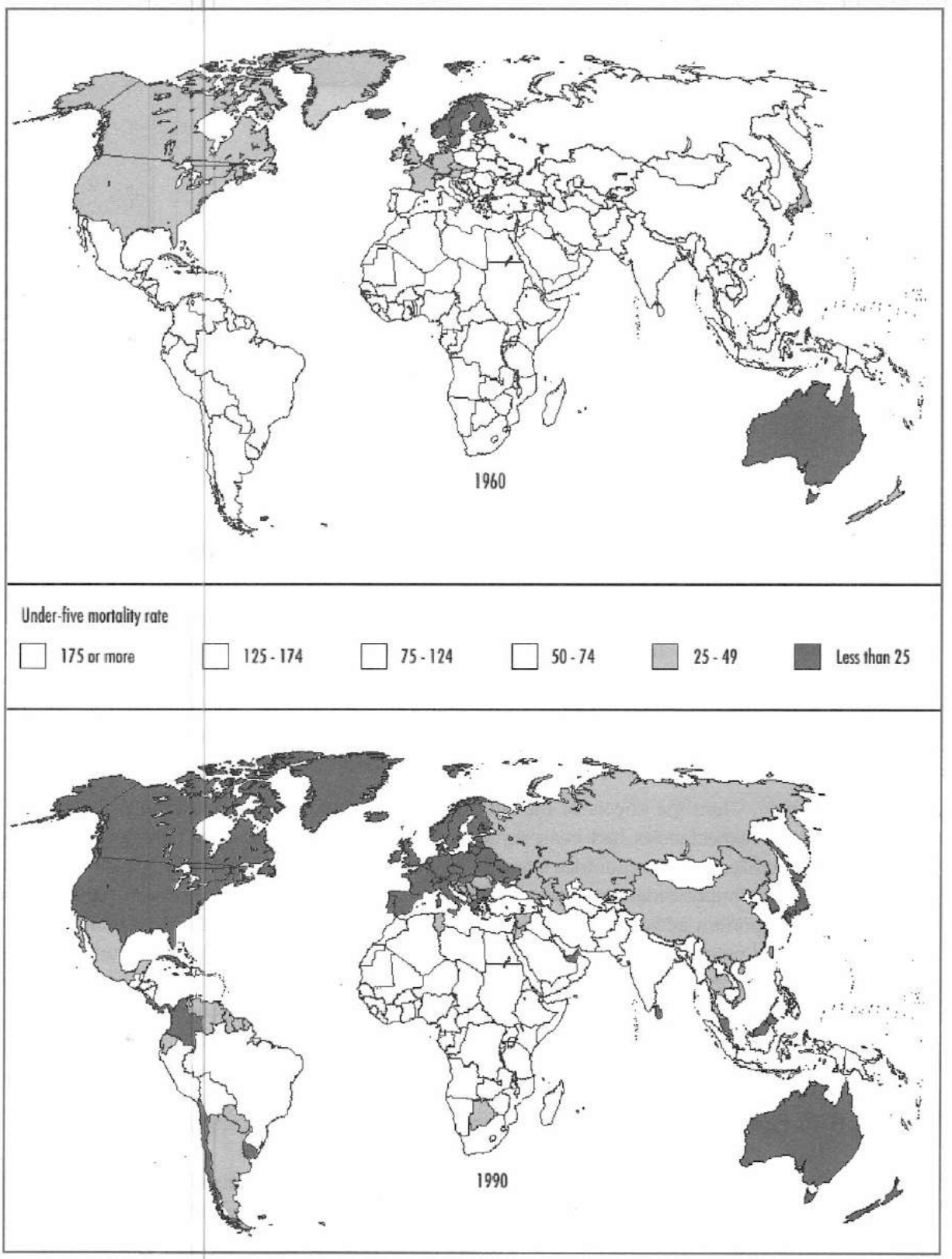
Variation in resources available for healthcare between countries

2.10 There is, in general, a strong association between life expectancy and economic development.[13] Figure 2.5 plots life expectancy at birth in relation to gross national product (GNP) per capita.[14]

11 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.
12 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.
13 Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.
14 The GNP is the total value of all final goods and services produced for consumption in a country: it is a measure of a nation's total economic activity.

Figure 2.3:

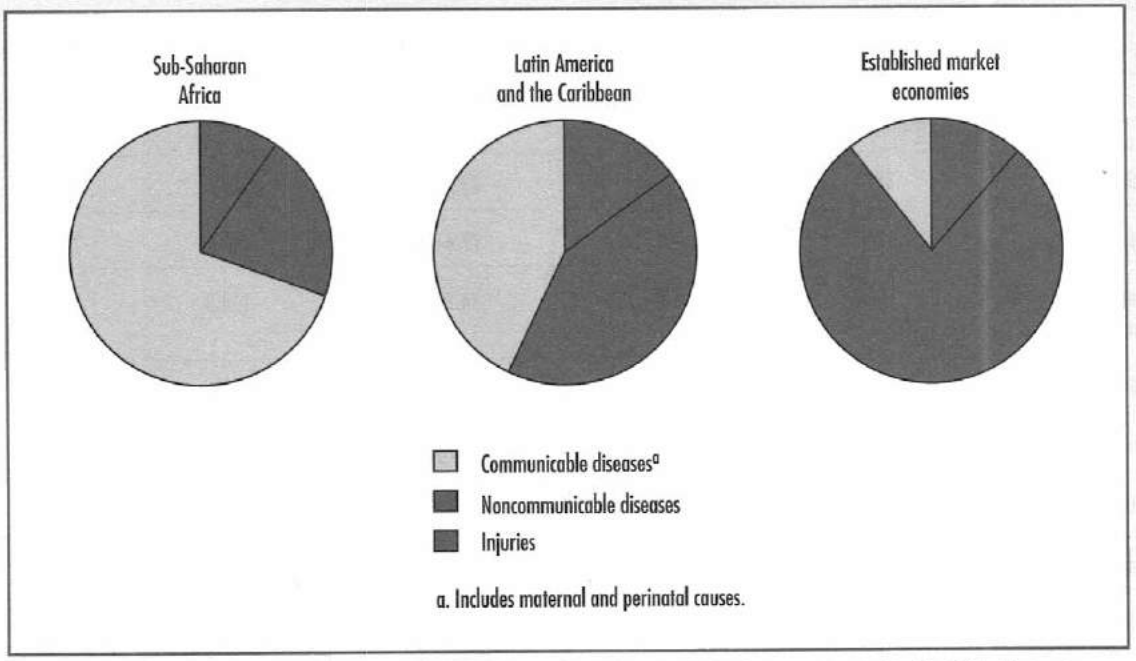
Child mortality by country, 1960 and 1990



Reproduced with permission from The World Bank (1993) **World Development Report 1993. Investing in Health,** Oxford University Press, New York.

Figure 2.4:

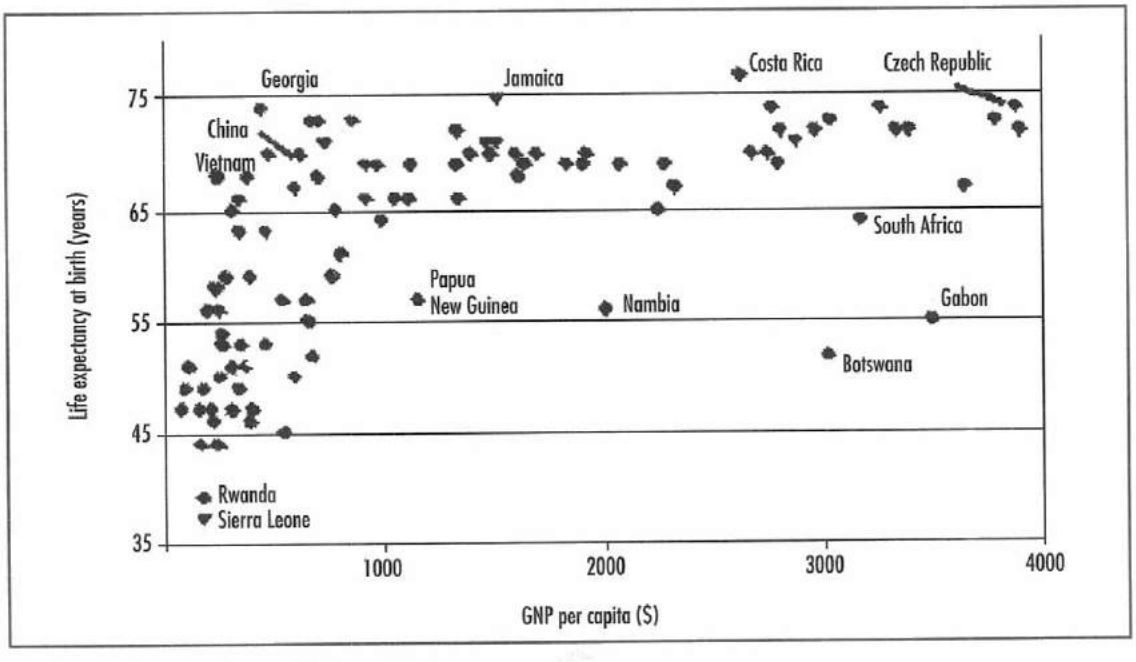
Distribution of disability-adjusted life years (DALYs) lost, by cause, for selected demographic regions, 1990 (percentage of total DALYs lost)



Reproduced with permission from The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

Figure 2.5:

Relationship between life expectancy at birth and gross national product per capita



Reproduced with permission from World Bank Publications.

Table 2.1

Expenditures on health and other health indicators in selected developed and developing countries

	Annual health expenditure per capita (internat. $[1])	Health expenditure as % GNP	Life expectancy at birth Males/females	Doctors /10^5 popn	Nurses /10^5 popn
United States	3724	13.7	73.8 /79.7	279.0	972.0
Japan	1759	7.1	77.6 /84.3	193.2	744.9
United Kingdom	1193	5.8	74.7 /79.7	164.0	497.0
Chile	581	6.1	73.4 /79.9	110.3	47.2
Brazil	428	6.5	63.7 /71.7	127.2	41.3
Cuba	109	6.3	73.5 /77.4	530.4	677.6
Afghanistan	89	3.2	45.3 /47.2	11.0	18.0
India	84	5.2	59.6 /61.2	48.0	45.0
Sri Lanka	77	3.0	65.8 /73.4	36.5	102.7
Uganda	44	4.1	41.9 /42.4	n/a	18.7
Sierra Leone	31	4.9	33.2 /35.4	7.3	33.0
Somalia	11	1.5	44.0 /44.7	4.0	20.0

Reproduced with permission from WHO (2000) **The World Health Report 2000. Health Systems: Improving performance.** WHO. Geneva and WHO Estimates of Health Personnel: Physicians, Midwives, Dentists and Pharmacists (around 1998) at http://makeashorterlink.com/?D2271283.

[1] International dollars' take into account the local purchasing power of the currency and in developing countries are thus generally higher than the expenditure in US$'s.

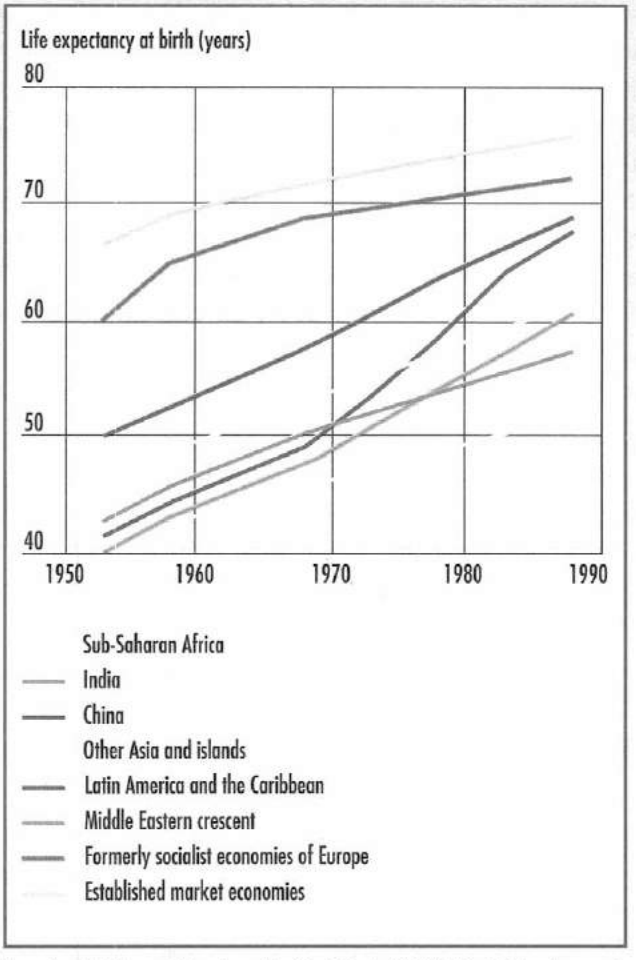
Though the relationship is not a simple one, the populations in countries with a low GNP per capita, and especially those with a GNP per capita of less than US$1000, tend to have much lower life expectancies than those in wealthier countries. Although there has been a substantial improvement in life expectancy over the last several decades in most countries,[15] there has been little change in the relative differences in life expectancy between regions of the world at different levels of economic development, as illustrated in Table 2.1 and Figure 2.6.[16]

2.11 The previous paragraphs have highlighted the wide differences in health between, and in some cases within, countries and pointed out the broad relationship between better health and more advanced socio-economic development. The level of expenditure that different countries devote to healthcare also varies widely. For example, it has been estimated that the US, which has approximately 5% of the world's population, is responsible for 50% of the annual global expenditure on healthcare.[17] In general, developing countries are able to devote a smaller proportion of their GNP to health than wealthier countries can. Furthermore, in absolute terms, the resources allocated are substantially less than in developed countries. This is reflected in the

15 Before the impact of the AIDS pandemic was reflected in life expectancy data (see paragraph 2.9).
16 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.
17 Bloom B (1999) The future of public health, **Nature**, 402: C63–4.

Figure 2.6:

Trends in Life Expectancy by Demographic Region, 1950–90



Reproduced with permission from The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

numbers of physicians and nurses per member of the population. For example, the number of physicians ranges from over 100 per 100,000 members of the population in more developed countries to less than 10 physicians per 100,000 members of the population in the least developed countries (Table 2.1).

2.12 Of course, the health of a population is determined not only by the resources devoted to healthcare and to preventive medicine, but also by investment in other important determinants of good health such as education, nutrition, water, sanitation and communication infrastructure. The lack of resources to develop these facilities, which are crucial if health benefits are to be sustained, further disadvantages developing countries. Even in those countries in which there are potentially more resources available to devote to infrastructure development, political leaders may sometimes have alternative priorities and allocate funds elsewhere.

The 10/90 disequilibrium: research expenditure and premature mortality

2.13 The disparity in expenditures on health research between developed and developing countries was highlighted in the 1990 report of the Commission on Health Research for Development.[18] This

18 CHRD (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.

group assessed the total funds that were being spent on research in different countries and examined the burden of ill health. Their analyses revealed a striking disparity between health needs and research expenditures. Using those countries with the lowest mortality rates as a benchmark, they proposed that differences from these rates in other countries represented potentially avoidable mortality. The amount of avoidable mortality[19] in developed and developing countries was calculated and compared to the estimated research expenditures on the respective health problems of each country. These calculations led to the estimates that 93% of the global burden of premature mortality is attributable to disease problems in developing countries but that about 95% of global expenditure on health research is directed at the disease problems of developed countries. Refinements of these estimates by the WHO Ad Hoc Committee on Health Research[20] supported the conclusion that the central problem in research on health is the '10/90 disequilibrium'. Namely, that of the US$ 50–60 billion spent world-wide each year on health research by both the private and public sectors, only 10% is devoted to the health problems of 90% of the world's population.[21] It is against such a background that research on health in developing countries must be considered.

2.14 The gross disparities in investment in research on health between countries are also reflected in the availability of those with appropriate training to conduct research on health. Despite the great need for research to determine the most effective interventions in developing countries, the indigenous capacity to conduct this research is severely limited. The lack of appropriate infrastructure, expertise and resources are major constraints. Externally-supported research that does not address this issue of development of capacity in research may greatly limit the long-term value of the research. In many respects such research is the equivalent of food aid, which does not provide the tools and skills to help the local population to become self-sufficient in growing their own food. Building capacity within developing countries will help those countries to set their own priorities for research and to conduct the most relevant research for local health needs.

2.15 As many developing countries have very limited resources, it is highly desirable that investments in healthcare focus on those interventions that are affordable, effective and accessible. This is best achieved by ensuring, so far as is possible, that health policy is evidence-based: only those interventions that are proven to be effective and affordable are introduced into the national health programme. To develop such an evidence base requires that the experience of other countries with particular interventions is taken into account. When the evidence is lacking, it will sometimes be necessary to conduct new or additional research in the relevant country. This will often be beyond a developing country's own resources and research which is externally sponsored may be the sole means of acquiring the necessary evidence.

The scope of externally-sponsored research

2.16 Whilst there is currently no central audit of research which is conducted in developing countries by external sponsors, organisations such as the US Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA) monitor the amount of research and development (R&D) conducted abroad. The FDA has recorded a 16-fold increase in the number of foreign clinical investigators conducting research on new medicines in the decade 1990–2000. Numbers grew from 271 in 1990 to 4,458 in 1999.[22] The number of

19 In terms of years of life lost due to premature mortality.
20 World Health Organization (1996) **Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options**, WHO, Geneva.
21 Global Forum for Health Research (1999) **The 10/90 Report on Health Research 1999**, Global Forum for Health Research, Geneva.
22 DHHS Office of Inspector General (2001) **The Globalization of Clinical Trials. A Growing Challenge in Protecting Human Subjects**, Office of Evaluation and Inspections, Boston.

Table 2.2

Growth in domestic US R&D and R&D overseas

Year	Domestic US R&D ($ M)	US R&D Abroad ($ M)
2001	23,640.0	6,862.0
2000	19,986.7	5,692.2
1999	18,499.3	4,219.6
1998	17,222.5	3,839.0
1997	15,516.6	3,492.1

Source: PhrMA (2001) **Pharmaceutical Industry Profile 2001: Table 1: Growth in Domestic US R&D and R&D Abroad, Ethical Pharmaceuticals, Research-based pharmaceutical companies, 1970–2001.**

countries, monitored by the FDA, in which clinical investigators conducted research increased nearly three-fold from 28 to 79 for the same period, with the largest growth occurring in Latin America and Eastern European countries.[23]

2.17 In its Annual Survey for 2001, PhRMA gave a detailed account of R&D by research-based pharmaceutical companies. Although this showed recent dramatic growths in the investment and proportion of US R&D conducted abroad (Table 2.2), the proportion of overall R&D conducted in developing countries remains small, with the highest proportion of research carried out in the developing world taking place in Latin America (Table 2.3).

2.18 Audits of international research activity on specific diseases have also been conducted. For example, the Unit for Policy Research in Science and Medicine (PRISM) of the Wellcome Trust conducted an audit of malaria research.[24] Expenditure dedicated to research on malaria was found to be low compared with other areas of disease. For example, while the UK alone spent over $200 million on research on cancer in 1993, total expenditure for research on malaria *worldwide* was only $84 million. Analysis of research publications showed that active research was taking place in many areas of basic research into malaria, such as the mechanisms of action of medicines and disease transmission, but that there was less research in other areas, such as means of providing antimalarial treatment to populations in developing countries.

2.19 However, since the second half of the 1990s, this picture of international research activity has been reconfigured somewhat. This is due in part to the growing number of collaborations between the corporate and public sectors in the form of global public-private partnerships (GPPPs). These developed from recognition of market and 'public' failures in international public health and have allowed major investments in the area. Examples include the Medicines for Malaria Venture (MMV), one of the first public-private partnerships which found its origins in the failure of the market system to provide the required incentives for wide-scale R&D in new medicines for malaria.

23 DHHS Office of Inspector General (2001) **The Globalization of Clinical Trials. A Growing Challenge in Protecting Human Subjects**, Office of Evaluation and Inspections, Boston.

24 Anderson J, MacLean M and Davies C (1996) **Malaria Research. An Audit of International Activity**, Unit for Policy Research in Science and Medicine (PRISM), Wellcome Trust, London.

Table 2.3

US funded R&D conducted abroad by geographic area in 1999

Geographic area	Amount (US$ mil.)	Share (%)[1]
Canada	451.2	9.2
Latin America (inc. all Caribbean nations)	78.5	1.6
Western Europe (EC, European Free Trade Association and Switzerland)	3,569.2	72.9
Central and Eastern Europe (inc. ex-USSR)	21.6	0.44
Middle East (inc. Turkey)	3.5	0.07
Africa	4.1	0.08
Asia/Pacific (from Pakistan to SE Asia inc. China, Taiwan, and the Koreas)	19.7	0.40
Japan	711.1	14.5
Australia and New Zealand	45.4	0.93
Total	**4,904.2**	

[1]Percentages do not add up to 100 because of rounding.

Source: PhrMA (2001) **Pharmaceutical Industry Profile 2001: Table 9: R&D Abroad by Geographic Area, Ethical Pharmaceuticals, Company-financed, U.S.-Owned Research-based Pharmaceutical Companies, 1999.**

2.20 As in developed countries, a very wide range of research related to healthcare is conducted in developing countries, the majority of which is externally sponsored. The spectrum ranges from laboratory research into the causes of disease, through clinical research involving human participants which aims to determine the safety and efficacy of novel interventions, to feasibility and operational research, which is designed to determine if and how effective treatment can be delivered to the broader patient population (see Box 2.1). The various types of research conducted are discussed further in Appendix 2.

Setting priorities for research

2.21 The question of how a country sets its priorities for research in healthcare is particularly important in developing countries because national resources for research are generally very limited. The setting of national priorities for research is a complex process involving national and international research objectives, institutions and individuals. Clearly, the greater the capacity of a country to conduct its own research and to have systems in place to determine its own priorities, the easier it will be to ensure that the questions posed by externally-funded research are appropriate and relevant to national health needs. It will be more difficult for government and external sponsors to collaborate effectively if there is no clear picture of the priorities for research within a country.

2.22 The capacity of developing countries to set their own priorities for research varies widely. Some countries make use of WHO's recommendations by adopting those parts that are relevant to

BOX 2.1 Examples of the kinds of research conducted in developing countries

Basic research

A genetic transformation system for the mosquito *Anopheles stephensi*, a major carrier of malaria in urban areas of the Indian subcontinent has now been developed.[1] Such developments in understanding the interactions between malaria parasites and the mosquito vectors of malaria will allow further research into the molecular aspects of malaria parasite transmission and new control mechanisms for the disease. Researchers at Michigan State University are already investigating the production of genetically engineered strains of mosquito that fail to transmit the pathogen, which may ultimately allow the wild population to be replaced by this 'innocuous' strain.[2]

Epidemiological research

A study was initiated in the Soroti District of Uganda following an outbreak of *Trypanosoma brucei rhodesiense* sleeping sickness. The disease had previously been absent in the district. However, it coincided with large-scale livestock restocking activities in the area and the research investigated the role of the cattle in the origins of the outbreak, as they can form important reservoirs for the parasite.[3] This project was supported by the UK MRC and the DFID Animal Health Programme.

Natural history of diseases

In 2000, the UK MRC funded a 3-year study in north eastern Tanzania. This programme is examining how the pattern of malarial infection is affected by changes in the intensity of malaria transmission due to the effects of altitude on mosquito survival.[4]

Social and behavioural research

Members of the Kigoyera Parish in western Uganda who had undergone HIV testing and counselling were interviewed about their sexual behaviour. This study, which was supported by Germany, was conducted to examine the effectiveness of HIV counselling and testing in reducing high-risk sexual behaviour in this rural population.[5]

Clinical research

The US company, VaxGen is currently conducting a phase III placebo-controlled, double blind trial of its HIV vaccine in Thailand. The participants in research are HIV-negative injecting drug users with a high risk of blood-borne HIV transmission. The trial is designed for a total of 2500 volunteers and is taking place in 17 methadone clinics under the direction of the Bangkok Metropolitan Administration.[6]

Feasibility studies

It was proposed that Zimbabwe adopt a visual inspection with acetic acid (vinegar) as a first line low cost screening method for cervical cancer. A feasibility study was planned in two districts of Zimbabwe to assess the feasibility of integrating the inspection into existing primary health care facilities.[7] This research was supported by the Ministry of Health of Zimbabwe and the United Nations Population Fund (UNFPA).

BOX 2.1 *Continued*

Health systems research

The International Trachoma Initiative (ITI)[8] is dedicated to eliminating blindness from trachoma. This is a preventive and treatment-based programme, involving the donation of the medicine Zithromax (Azithromycin) and supplemented by surgical techniques and public hygiene education. The programme is then followed up to determine its effectiveness. To date, studies have been conducted in Morocco and Tanzania to assess its success.[9]

1 Catteruccia F, Nolan T, Loukeris TG, Blass C, Savakis C, Kafatos FC *et al* (2000) Stable germline transformation of the malaria mosquito *Anopheles stephensi*, **Nature**, 405: 959–62.
2 Scientists are racing to create a genetically modified 'super mosquito' that will destroy malaria ..., **Sunday Times**, 1 July 2001.
3 See Fevre EM, Coleman PG, Odiit M, Magona JW, Welburn SC and Woolhouse ME (2001) The origins of a new Trypanosoma brucei rhodesiense sleeping sickness outbreak in eastern Uganda, **Lancet**, 358(9282) 625–8.
4 See http://makeashorterlink.com/?C2684108.
5 See Kipp W, Kabagambe G and Konde-Lule J (2001) Low impact of a community-wide HIV testing and counseling program on sexual behavior in rural Uganda, **AIDS Education and Prevention**, 13(3) 279–89.
6 See 'VaxGen Clinical Trials' at http://www.vaxgen.com/vaccine/index.html.
7 http://www.south-south.org/Word_pdf/Sstories/Jinja/cervical%20cancer.pdf.
8 The ITI was established by Pfizer Inc. and the Edna McConnell Clark Foundation.
9 Access to medicines in the developing world through partnerships, comments by Chuck Hardwick, Senior Vice President, Pfizer Inc., WHO/WTO Workshop on Differential Pricing and Financing of Essential Drugs, 10 April 2001, Høsbjør, Norway.

health policy in their own country.[25] Others have used approaches developed over the past decade to systematise the setting of priorities in research on health. The broad aim of these initiatives has been to enable decision makers to make more informed decisions in their allocation of limited research funds. The specific objective has been to ensure that a given investment in research has the greatest impact on the health of the largest number of people in the community. However, many developing countries do not have the resources to make a comprehensive assessment of the prevalence and effects of disease within their borders.

2.23 Essential national health research (ENHR) is a strategy which has been used by several developing countries to organise and manage research related to healthcare through systematic priority setting.[26] Key criteria for the selection of research areas for priority include economic impact, cost effectiveness of future interventions, effect on equity, social justice and acceptability, and contribution to the strengthening of capacity in research. Some 18 countries have developed ENHR strategies including South Africa, Thailand, Pakistan and Tanzania. The implementation of these strategies will depend on several factors, not least research capacity, the availability of adequate infrastructure and the availability of funding.

25 WHO's recommendations about priority areas are formulated by The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), its research programmes and by the Joint United Nations Programme on HIV/AIDS (UNAIDS). More than 50 developing countries have additionally adopted ENHR strategies to support action promoting equity in health. Countries have used a variety of mechanisms to implement the ENHR strategy but which share a common link between research and policymaking. For example, Jamaica has had an ENHR Task Force in place since 1995 which is formally recognised by the Ministry of Health and brings together representatives from the Ministry, university-based units, and the Planning Institute of Jamaica in promoting and advocating ENHR. Uganda has a national task force which consults on research priorities with senior government officials and researchers, district planning committees and health teams, along with community members. In addition, Uganda's ENHR co-ordinating team is trying to develop the capacity to set research priorities and carry out relevant research at the district level, to allow better definition of district-specific problems and the contribution of local communities in determining such. (See Neufeld V and Johnson N (2001) Forging Links for Health Research. Perspectives from the Council on Health Research for Development, International Development Research Center, Canada for further details of country-specific initiatives.)
26 The concept of ENHR was advanced by the Commission of Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991). The Council on Health Research for Development (COHRED) has further developed the approach through practical application in several countries and provides the current mechanism of support for ENHR at the country and global level.

2.24 Overall, progress in implementing strategies for ENHR has been slow and uneven for a number of reasons, including ineffective strategies for communication and weak national funding arrangements. The sociopolitical realities of some countries or parts of countries have also been cited as problematic in establishing effective links between research and policy, whilst international organisations involved in research on health may also significantly influence what happens within a recipient country.[27] It has been suggested that these strategies for priority setting have only had an impact in countries such as Thailand where some national funding has been committed to subsequent implementation.[28] In countries where nearly all research related to healthcare is externally funded, the priorities for research have been largely set by the external sponsors.

2.25 In such circumstances, questions arise about the extent to which external sponsors are guided by national priorities when making decisions about research sponsorship. External agencies, including other national governments, research councils, private sponsors, non-governmental institutions or agencies and pharmaceutical companies, sponsor the majority of research related to healthcare in developing countries. Many funding agencies have their own approaches for the identification of areas which merit support. As many external sponsors fund at the level of individual researchers rather than institutions, it is important that there is awareness of priorities for national research at the local level.

2.26 Governmental bodies such as the UK Medical Research Council (MRC) and UK Department for International Development (DfID), US Centers for Disease Control (CDC), the European Commission (EC) (see Box 2.2), international agencies and pharmaceutical companies generally support or undertake applied health-driven research, as do the large charities (for example, the Bill and Melinda Gates Foundation and the Wellcome Trust) (see Box 2.3). Scientific excellence is the first criterion used by most sponsors of research. Additional criteria for funding include the relevance of research to the host countries' needs; the practicalities of undertaking the proposed research; and the likelihood of the research results being taken up in the host country for the improvement of health. Several sponsors have advisory panels with members from both developed and developing countries to assist them in identifying areas of priority for support in consultation with the relevant communities.[29]

2.27 Several GPPPs have also been established to address the public health problems of developing countries, some of which are concerned with research or have a research component.[30] Other GPPPs are focused on the development of products such as the International AIDS Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI) and MMV; others are concerned with the donation of specific products such as the Malarone (antimalarial medicine) donation programme or broader programmes as in the Case of Global Alliance for Vaccines and Immunization (GAVI) (see Box 2.4). GPPPs, such as MMV and IAVI, bring together the substantial resources of public and private sector organisations to develop vaccines and medicines for common and serious diseases such as AIDS, TB and malaria.[31] Research on these diseases will clearly be relevant to the national research priorities of the majority of developing countries.

2.28 The United Nations Development Programme/World Bank/WHO 'Special Programme for Research and Training in Tropical Diseases' (TDR) is one of the international agencies that has

27 Chunharas S 'Linking research to policy and action' in Neufeld V and Johnson N (2001) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, IDRC, Ottawa.
28 Binka F (2001) Personal communication, Navrongo Health Research Centre.
29 For example, the UK Medical Research Council and the Wellcome Trust.
30 There is some disagreement about what constitutes a public–private partnership but a good definition is thought to comprise three key components: involvement of at least one private profit-seeking organisation with at least one not-for-profit organisation; shared efforts and benefits; commitment to the creation of a social value (improved health), especially for disadvantaged countries. See Reich M (2000) Public–private partnerships for public health, **Nature Medicine**, 6(6) 617–20.
31 Lucas A (2000) Public–private partnerships. Illustrative examples, **Workshop on Public-Private Partnerships in Public Health**, 7–8 April 2000, Endicott House, Dedham, Massachusetts.

BOX 2.2 Examples of governmental bodies funding research in developing countries

UK Medical Research Council (MRC)

The UK MRC works closely with DfID to fund research relevant to priorities in healthcare in developing countries. Research funded ranges from basic to clinical research, with particular emphases given to poverty reduction and the need to foster local capacity in research through in-work training and collaborative partnerships with developing countries. The MRC has laboratories in The Gambia which undertake research programmes spanning HIV/AIDS, TB, malaria, reproductive health, viral diseases, respiratory infections, non-communicable diseases and nutrition, each having basic, clinical and epidemiological components. Additionally, the MRC has an integrated multidisciplinary research programme for the study of HIV-1 in Uganda and a malaria programme in Tanzania. The MRC's Human Immunology Unit at Oxford University has an established programme for the preparation and trials of HIV vaccines in the UK and Kenya. Phase I trials of a resultant DNA vaccine against HIV are underway in Oxford and Nairobi, Kenya.[1]

European Commission Programme of Action to combat HIV/AIDS, malaria and tuberculosis

In February 2001, the EC approved a Communication outlining a programme for action on HIV/AIDS, malaria and tuberculosis which would build on existing EC investments in research on these major diseases.[2] In terms of research and development, this emphasised targeted action for increased public support for R&D, involving continued and increased support for basic and strategic research with improved co-ordination at European and international levels, along with the creation of a European Clinical Trials platform to increase the number, efficiency and coherence of clinical trials conducted by the public and private sectors, and involving developing countries. Emphasis was also given to developing expertise in research in terms of increasing support to a range of research activities, giving emphasis to gender balance and poverty reduction and ensuring appropriate ethical standards and review systems are in place. Support would also be provided to developing countries to allow them to host and conduct large-scale population trials. The need to develop an incentive package to increase private investment in R&D for new products to tackle major communicable diseases in developing countries was also highlighted.

1 For more detailed information about the MRC's programmes in developing countries see: http://makeashorterlink.com/?C2684108.

2 See European Commission (2001) **Communication from the Commission to the Council and the European Parliament. Programme for Action: Accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction** at http://makeashorterlink.com/?I66F21E5.

sought to promote public-private partnerships, and to assist pharmaceutical companies in the late stage of product development. Acting as a broker linking academia, governments, industry, health professionals and affected communities, TDR has been involved in the implementation of field trials and the licensing out of new products, or new uses for existing products.[32]

Pharmaceutical R&D in developing countries

2.29 Most of the collaborative research undertaken by pharmaceutical companies in developing countries involves clinical trials. Priorities for national research may be considered to have little

32 Examples are multi-drug therapy for leprosy, ivermectin for onchocerciasis, eflornithine for African trypanosomiasis, artemether for malaria, praziquantel combinations for schistosomiasis and intestinal parasites, and more recently, miltefosine for visceral leishmaniasis, and artesunate suppository, medicine combinations and lapdap for malaria, among others Morel CM (2000) Reaching maturity – 25 years of the TDR, **Parasitology Today**, 16(12) 522–8.

relevance by a company that wishes to test a new medicine. Instead, the criteria for selecting a particular country for trial include the availability of suitable participants, the availability of high quality collaborators, and appropriate infrastructure for delivery of clinical care to the participants. The national priorities for research related to healthcare identified by a host country may have little bearing on where a company decides to locate its clinical trials. However, some companies such as GlaxoSmithKline (GSK) have several R&D projects to develop medicines for the treatment of diseases prevalent in developing countries (see Box 2.5). In some instances, the diseases are also relevant to developed country markets while in others, the research sponsorship may be altruistic.

BOX 2.3 Examples of charities funding research in developing countries

Bill and Melinda Gates Foundation

In 2000, the Foundation paid and awarded grants totalling US$1240 million for global health projects. Grants awarded included funding for the development of a vaccine for leishmaniasis, funding for a feasibility study to improve the manufacturing and delivery of vaccines in Russia, support for research aimed at the reduction of child mortality and funding to promote the discovery and development of antimalarial medicines.[1]

The Wellcome Trust

The Trust has three international programmes: International Biomedical, Tropical Medicine and Population Studies programmes.[2] The Trust spent £72.2 million on international research during 1999/2000. This included research into infectious and non-infectious human diseases and veterinary problems affecting developing countries, with research primarily conducted in South-East Asia and Kenya. Several project grants were awarded as part of the Non-communicable Disease Initiative in the areas of mental health, stroke and hypertension in Africa, Latin America and Southern Asia, and additionally, a major programme grant was given in India to explore the role of maternal nutrition and the development of insulin resistance in offspring.[3]

1 See http://www.gatesfoundation.org/.
2 Within its three international programmes, the Trust awarded a variety of fellowships and research and career awards.
3 Material taken from The Wellcome Trust Annual Review 1999/2000 at http://www.wellcome.ac.uk/en/1/awtpubreparvr00int.html.

2.30 Where an external agency has its own priorities for research on healthcare, provided that these coincide with those of the recipient country, there is potential for mutual benefit. If the agendas do not coincide, then the financial influence of the external agency may become the driving force (see paragraph 2.24). The principal manner in which a research sponsor might distort the priorities for research in a developing country is through the funding of research that has no direct benefit to its individuals nor to the society as a whole. Examples include the study of the natural history of a disease, a clinical intervention, a diagnostic process or the removal of tissues for research in a developed country. The example of the research on Burkitt's lymphoma in Africa (see Box 2.6) illustrates the issues which can arise when a researcher pursues a study of legitimate interest but which does not address a priority for healthcare in the host country. However, such research can offer considerable indirect benefits to host countries in the developing world because of the potential for strengthening the national capacity in research, in the form of improved infrastructure and training.

2.31 Despite the difficulties that developing countries may face in achieving the effective implementation of national priorities for research in healthcare, there is a strong case to be made for setting research priorities together with a robust mechanism for scientific review and ethical review of any proposed research (see Chapter 8). How this is managed will depend on the resources available in each country. **We therefore endorse the view of the Commission on**

BOX 2.4 Global Alliance for Vaccines and Immunization (GAVI)

GAVI has identified three priorities for its initial vaccine development efforts: pneumococcal conjugate vaccines for pneumonia and meningitis, rotavirus oral vaccines for severe diarrhoea and meningococcal A (or A/C) conjugate vaccines for meningitis. These products were selected because of their potential impact on children's health and because availability and use could be predicted in 5–7 years.[1]

1 See http://www.vaccinealliance.org/reference/ update_ agendas.html for further details about GAVI's agenda to accelerate the development and introduction of these vaccines.

BOX 2.5 GlaxoSmithKline (GSK)

GSK has more than 20 active R&D projects for medicines to treat diseases prevalent in developing countries. It has been researching vaccines for HIV, TB and malaria, has three anti-malarial products at various stages of development and clinical projects are underway with a new combination product and a novel protease inhibitor for HIV/AIDS, along with research efforts to discover medicines with novel mechanisms. GSK has an R&D programme to develop a Hepatitis E vaccine, a disease prevalent in South-East Asia. It also has a randomised clinical trial in children of Zentel (Albendazole) to assess the impact of early de-worming on long-term childhood survival.[1] In addition, GSK has more than 30 external partners and alliances for diseases relevant to developing countries. Paediatric clinical trials of a malaria vaccine began in the Gambia in May 2001 in partnership with MVI. This is the first of a series of three planned trials. GSK is also working in partnership with academic institutions and with NIH funding to identify novel targets for antimycobacterial chemotherapy and developing new compounds suitable for pre-clinical evaluation for TB.[2]

1 GlaxoSmithKline (2001) **Facing the Challenge. Our contribution to improving healthcare in the developing world**, GlaxoSmithKline plc, Greenford.

2 European Federation of Pharmaceutical Industries and Associations (EFPIA) (2001) **Non-exhaustive list of initiatives carried out by the pharmaceutical industry to combat health problems in the developing world**, EFPIA, Brussels.

Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991) that all countries should set priorities for research into healthcare. However, given that in many developing countries, most research on healthcare is externally funded, we consider that sponsors have a responsibility to consider their own research priorities in the light of national priorities which exist in host countries.

2.32 We do not take the view that all externally-funded research should fall within nationally defined priorities, since all research contributes to the development of local skills and expertise in research, quite apart from the inherent value in diversity of research. However, there is a careful balance to be drawn. The inherent inequalities of power and advantage between developed and developing countries require that particular care is needed to restrain any tendency on the part of the sponsor to pursue their interests to the detriment of those of the host country. **We therefore recommend that when research funded by external sponsors is proposed which falls outside the national priorities for research into healthcare set by a host country, those proposing the research be required to justify the choice of the research topic to the appropriate research ethics committees in both the host and sponsoring countries.**

Developing new interventions

2.33 As we have seen, socio-economic development is usually, although not always, associated with an increase in life expectancy and reductions in the many causes of morbidity. In general, improvements in healthcare can be brought about more rapidly than improvements in socio-economic status, although the two are closely linked. While it is clear that poverty is a major

determinant of ill-health, there is increasing evidence that poor health significantly impedes development.[33] Consequently, there has been a drive to find more effective medicines and vaccines for the treatment and prevention of some of the major diseases afflicting people in developing countries. The development of such interventions may have the dual effect of directly promoting improved health and leading to further health gains through the impact that such improvements will have on socio-economic development. However, some have argued that such a focus may distract attention from interventions directed at reducing socio-economic inequalities as the fundamental means of improving health.

BOX 2.6 Burkitt's lymphoma

Burkitt's lymphoma is a childhood tumour first described in 1958. The disease is rare in Western countries but endemic to African countries such as Kenya and Uganda. Burkitt's lymphoma accounts for over half of all childhood cancers in Africa, affecting about two in 100,000 children each year. However, it is a rare cause of death when compared to diseases such as malaria (which causes to 20% of childhood deaths in the worst affected areas).

Despite its rarity, Burkitt's lymphoma was comprehensively researched in the 1950s and 60s in Africa. A team of researchers led by Burkitt charted its occurrence from Uganda to South Africa, determined the altitude-dependency of the disease, its common occurrence in malaria-endemic areas and its association with the presence of antibodies to the Epstein-Barr virus. The value of this early research to subsequent cancer research and treatment is now well recognised.[1]

1 Magrath IT (1991) African Burkitt's Lymphoma. History, biology, clinical features and treatment, **American Journal of Paediatric Hematology/ Oncology**, 13(2) 222–46.

2.34 Because budgets for health are very restricted in many developing countries, interventions that are to be widely deployed must be affordable. Ideally, they would be provided or purchased locally at low cost. Examples of such interventions include insecticide-impregnated bed-nets to protect against malaria, and vitamin A supplementation to reduce child mortality. In areas in which malaria is highly prevalent, it has been shown that the provision and use of insecticide-impregnated bed-nets, which cost less than $10 each, reduce child mortality rates by 20% or more.[34] In large areas of the world where there is vitamin A deficiency, the administration of a dose of this vitamin to children every four to six months, at a cost of a few pence a dose, has also been shown to reduce total child mortality rates by around 20% (although greater costs are incurred in setting up a mechanism to ensure that children regularly receive vitamin A).

2.35 In relatively common use are some interventions that may be costly but which may be supplied at subsidised prices, or free of charge, by donor agencies or organisations from developed countries. Increasingly, international agencies have been negotiating with pharmaceutical companies to obtain concessions to supply medicines and vaccines at 'affordable' cost in developing countries through tiered pricing schemes or, in some instances, by donations of products for such use. These issues are discussed further in Chapter 9. Examples of these concessions include many vaccines and the very substantial donations of medicines that have been made by pharmaceutical companies for the treatment of river blindness (onchocerciasis) with ivermectin, elephantiasis (lymphatic filariasis) with ivermectin and albendazole, trachoma with azithromycin and malaria with Malarone®. Donor agencies have also made contraceptives widely available at little or no cost in developing countries and large numbers of condoms have been supplied in an attempt to slow the spread of HIV infection.

33 Sachs and colleagues have argued strongly the latter point in respect of malaria and other diseases. For example, see Gallup JL and Sachs JD (2000) **The Economic Burden of Malaria. CID Working Paper No. 52**, John Luke Gallop, Jeffrey D Sachs and the President and Fellows of Harvard College at http://www2.cid.harvard.edu/cidwp/052.pdf

34 Lengeler C, Armstrong-Schellenberg J, D'Allesandro U, Binka F and Cattani J (1998) Relative versus absolute risk of dying reduction after using insecticide-treated nets for malaria control in Africa, **Tropical Medicine and International Health**, 3(4): 286–90.

2.36 We have noted above that for many infectious diseases affecting predominantly those in developing countries there are either no effective treatments or vaccines available, or there is a need to develop improved or new interventions. Recent advances in microbiology and biotechnology may lead to the development of new vaccines within the next decade. Not all vaccines will provide protection against the target diseases and rigorous evaluation will be needed before their use in public health programmes. Advances in biological knowledge will similarly expand the range of potential diagnostic tests and therapeutic interventions, and these will also require careful evaluation before widespread introduction and use.

2.37 There are, of course, substantial costs associated with bringing a new medicine or vaccine into use for public health.[35] In the case of most new medicines, the development costs will be borne by a pharmaceutical or biotechnology company. In the case of vaccines, global public-private partnerships such as IAVI promise to play a key role in the development of new products directed at the developing world. There are few public institutions, even in the developed countries, that are in a position to underwrite the heavy costs of developing compounds discovered in their own laboratories to the point of marketing approval. These costs and the time-scales of the development process will be reflected in the prices placed on new medicines by the companies producing them.[36] New medicines are priced to cover not only the costs of their own development, but also the costs of those potential treatments that fail in development. It is currently estimated that only one out of every 5,000 or so compounds discovered will reach the market place.[37] Of these, only a few will be major 'blockbuster' medicines which produce very high income for a company. In addition, the discovery of new medicines is based largely on the application of new technologies which requires very considerable investment in R&D. A significant proportion of the sales revenue of a major pharmaceutical company (15–18% of sales in the UK industry) is therefore ploughed back into R&D.

2.38 The high costs of development for new medicines means that the pharmaceutical industry has generally invested in R&D for medicines for diseases which affect large numbers of people who can afford to pay for treatment, such as heart diseases, respiratory diseases, inflammatory diseases and cancers. Through the development of successful medicines for these diseases, companies aim to recover their costs, invest in further R&D and return profits to the shareholders. Consequently, diseases which affect only small numbers of patients, or which affect large numbers of patients who have no resources in their healthcare system to buy new medicines, have tended to be ignored. The small market (in terms of purchasing power, rather than population size) cannot support the effort required to bring a medicine from the laboratory to the clinic.

2.39 These are the so-called 'neglected diseases' and include many of the major tropical diseases, as well as diseases which only affect small numbers of people in developed and developing countries. For example, Table 2.4 lists the limitations of the current medications available to

35 Pharmaceutical companies have estimated this cost to be in excess of $500 million. In contrast, a recent study by Tufts Center for the Study of Drug Development put the cost of the development of a new prescription medicine at $802 million (see Tufts Center for the Study of Drug Development press release 'Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at $802 million at http://www.tufts.edu/med/csdd/images/NewsRelease113001pm.pdf). Public Citizen claimed that the figure was actually in the order of $110 million (see Public Citizen (2001) **Rx R&D Myths: The Case Against the Drug Industry's R&D 'Scare Card'**) and that the estimate of pharmaceutical companies was unreliable as it included the cost of all failed medicines, the expense of using money for research into medicines rather than other investments and did not account for the tax reductions companies obtain for R&D. However the validity of Public Citizen's claims have been challenged and attributed to'methodological shortcomings' (see Ernst and Young (2001) **Pharmaceutical Industry R&D Costs: Key Findings about the Public Citizen Report**).

36 However, other factors will also come into play in the determination of pricing. The longer the development time for the new product, the shorter the unexpired patent life when it reaches the market. The period of exclusive sales during which development costs can be recovered is therefore shorter.

37 Spilker BA 'The Drug Development and Approval Process', PhRMA at http://www.phrma.org/searchcures/newmeds/devapprovprocess.phtml. This is based on research carried out by Tufts Center for the Study of Drug Development which looked at medicines approved for the period 1993–1995 and found that only five in five thousand compounds entering preclinical testing reached testing in humans and only one in five of those tested in humans was approved for sale.

Table 2.4

Limitations of medicines for malaria

Medicine	Year of approval or use	Limitations
Quinine	1800s	Difficulties of use and effectiveness due to long treatment regimen and safety issues (e.g. tinnitus).
Chloroquine	1947	Increasing levels of parasite resistance have developed to this treatment.
SP (Fansidar)	1969	Increasing levels of parasite resistance have developed to this treatment and there are some side effects.
Artemisinins	1970s onwards	Difficulties of use and effectiveness as a single agent related to short half-life and long treatment regimen. Primarily promoted for use in combinations with other treatments, but this generates issues of compliance. Limited manufacture to the standards of good manufacturing practice. Some outstanding safety concerns but clinical experience on the whole is positive.
Mefloquine	1985	Relatively expensive, in some areas there is parasite resistance to this treatment and there are concerns about its safety.
Halofantrine	1988	Extremely expensive, some forms of malaria are resistant to this treatment and there are serious cardiotoxicity-related concerns about its safety.
Malarone	1996	Prohibitively expensive. Efficacious but there is the potential for forms of malaria to become resistant to this medicine. There is already resistance to individual components of the combination medicine.
Co-artemether	1998	Relatively expensive. Efficacious but there is the potential for resistance to develop.

treat malaria, a disease which was estimated to cause the loss of 45 million DALYs in 1999.[38] In 1996, the market for antimalarials was estimated at US$100–200 million while the market for antibacterials was over US$16,000 million (three products had sales of over US$800 million). While only one to two antimalarials are developed each decade, three to four new antibacterials reach the market each year. Moreover, of the antimalarials that have been developed, many cannot be afforded by patients in developing countries and are largely limited to the tourist market. Recently, however, as we have seen, there have been some promising developments in the area of public–private partnerships (see paragraph 6.27).

2.40 Pharmaceutical companies, encouraged by international agencies, are also starting to look for more economical, but effective, ways of using existing medicines to control diseases such as HIV/AIDS. For example, very recently, companies have begun to adapt their pricing structure to enable developing nations to receive medicines for HIV/AIDS at a fraction of the market price in the developed world, or at no cost, and there is increasing pressure on these companies to continue down this route. The World Trade Organisation (WTO) has recently clarified the position of its members with regard to their rights to implement the compulsory licensing of patented medicines when there is a public health emergency. Under such circumstances countries may manufacture generic[39] versions of patented medicines although countries without manufacturing capacity may not import these medicines.[40] However, the costs of many generic medicines will remain beyond the healthcare budgets of the majority of developing countries. In the case of antiretrovirals for

38 WHO (2000) Annex Table 4: Burden of disease in disability-adjusted life years (DALYs) by cause, sex and mortality stratum in WHO regions, estimates for 1999: 170.

39 Generic medicines are chemically the same as brand name medicines. They have the same characteristics (e.g. intended use, dosage, route of administration, safety, and quality) but are typically much lower in price than their branded counterparts.

40 World Trade Organization (2001) **Declaration on the TRIPS Agreement and Public Health (Doha Declaration)**, WT/MIN (01)/DEC/2, World Trade Organization, Geneva.

HIV/AIDS, even if the medicines were provided at no cost, the infrastructure required for delivery and monitoring side effects would be prohibitively expensive for most of the developing world.

2.41 The costs of evaluating a potential intervention for a tropical disease are substantial and, in general, cannot be covered by a developing country alone. For evaluation studies, pharmaceutical companies often donate products for trials and other costs involved may be met by international agencies. However, once efficacy has been established, the long-term supply of a product for public health use in a developing country may be very problematic if, as is often the case, the cost is beyond the resources available in the healthcare system. The slow deployment of vaccines against hepatitis B in developing countries and the restricted use of praziquantal against schistosomiasis are such examples.

2.42 However the cost of an intervention at the time of evaluation may fall substantially in due course (see Box 1.3). There have also been examples where beneficial interventions that are relatively costly can be used to argue the case for lowering, or subsidising, the price for developing countries. For example, in The Gambia, the demonstration of a strong protective effect of a vaccine against disease due to *Haemophilus influenzae* type b (HIB), has been an important factor in the more widespread promotion and subsidy of this vaccine, despite its substantial cost.

2.43 Not all 'new' interventions are expensive, however, and perhaps some of the most important advances have been made using products that are within, or close to, the resources that might reasonably be made available locally. For example, oral rehydration solution is cheap to produce and is highly effective at reducing mortality from diarrhoeal diseases.

The future

2.44 It can be expected that in the future there will need to be a radical change in the approach of the pharmaceutical industry to its R&D programmes and its investment in research. The first phase of the human genome project is now largely completed and it is reasonable to expect that increasing numbers of genes associated with, or perhaps causing, human diseases will be identified. This will provide research scientists with potential new molecular targets for the discovery of new medicines over the longer term. This approach has the potential to provide cures where existing medicines have only been able to alleviate the symptoms of a disease. However, many diseases will have multigene substrates, and selecting the optimal molecular target will be a substantial challenge.

2.45 However, it is possible that some of the currently 'common' human diseases will in fact be found to be a collection of different diseases, sharing a common appearance, but caused by different molecular mechanisms. Several common diseases may become collections of conditions affecting much smaller populations. Each condition may require a specific treatment. However, the cost of discovery, development and registration of new medicines for each condition may change, for example as clinical trials may change in size and complexity. It follows that for some diseases or sub-sets of disease improved treatments may only be available at higher prices. Providers of healthcare in the developing and developed world will need to adapt to the new approach. They will need not only to consider the cost of the medicines but also to take account of the cost-effectiveness and outcomes of new interventions, for instance reduced hospitalisation within the overall healthcare delivery system, as well as the more general economic benefits. In developing countries these new approaches will be difficult to implement, indeed, existing infrastructure is challenged to deliver current diagnostics and medicines. For the providers of healthcare, the provision of the infrastructure required to employ 'gene-based' or pharmacogenetic[41] medicines

41 Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to medicines.

effectively, i.e. screening and diagnostics, will present yet further challenges. For those wishing to carry out clinical trials, the costs may well become prohibitive if they must provide the necessary infrastructure to undertake such research. For these reasons, the pharmacogenetic approach to the development of medicines is unlikely to be available for developing countries for the foreseeable future.

Chapter 3

Social and cultural issues

Introduction

3.1 Developing countries are not a homogeneous group. They differ in many ways: culture, history, size of population and rate of growth, gross national product (GNP) per capita and levels of education (especially of girls and women). As discussed in the previous chapter developing countries also vary in terms of the technological and other forms of infrastructure they have in place, in their spectrum of health problems and in the quality and availability of healthcare. There are differences in the degree of social and economic inequality within countries. The degree of freedom of expression, recognition of human rights and extent of social harmony or disharmony are also highly variable. Rapid social and cultural changes are occurring in some developing countries following increased interactions with external cultures and technologies. As a consequence of all of these factors, it is inappropriate to regard developing countries as a single entity and their diversity must to be taken into account when issues arising from research related to healthcare are under consideration. In addition, there are significant variations within developing countries, especially those countries with a number of ethnic groups and significant differences in socio-economic status.

3.2 This chapter discusses the social and cultural contexts in which research in developing countries is conducted, providing a background to the discussion in the following section of the Report. It also highlights issues to which external sponsors and researchers should pay particular attention when research in developing countries is proposed. The interpretation of universal ethical principles in the light of social and cultural contexts is discussed in Chapter 4, while the implications of such contexts for the consent process are discussed in more detail in Chapter 6. While traditional systems of medicine are discussed in this chapter, the purpose of the discussion is to illustrate the contexts within which prospective participants may make decisions, rather than evaluating the effectiveness and evidence base underlying such systems.

Prevalence of alternative medical systems

3.3 One factor that may influence prospective participants in research is their understanding and use of traditional methods of healthcare and medical treatment, as well as the nature and level of their familiarity with evidence-based modern healthcare and research related to healthcare. There are a mix of modern medical and indigenous healthcare facilities in developing countries. For example, in the Middle East, parts of Africa, and South and South-East Asia versions of the Yunani system exist (derived from classical Arabo-Greek Galenic medicine) alongside modern healthcare and folk healing, as do the Ayurvedic system in India and the various Chinese therapeutic systems. This co-existence of different systems is also a feature of developed countries, as people increasingly seek complementary and alternative therapies, in addition to modern healthcare.

3.4 While there is much variation between continents and between regions within continents, local populations sometimes identify modern healthcare as especially valuable for acute conditions (following the successful use of antibiotics for eliminating infections rapidly). In contrast, long-term recurring problems may be ascribed to social, emotional, cosmic or religious causes, for which practitioners of alternative therapies are sought. This sometimes entails patients making choices along established lines: the first visit being to alternative medical practitioners or healers and subsequent ones to modern healthcare practitioners, or vice versa. This is a form of decision-making that may be unwelcome to researchers in both host and sponsoring countries. It is, however, a reality that in the long term it is more efficient to address than ignore.

BOX 3.1 Combining medical research and traditional healthcare

Ghana

Although there are effective medicines to treat malaria, many children in rural Africa who develop severe malaria die before they can receive help. In some such regions, the severe form of the disease (cerebral malaria which causes convulsions) is thought to be caused by evil spirits. As a result, children who have severe malaria with convulsions are often sent to traditional healers. It is also sometimes believed that such children should not receive injections, although they cannot take medications orally. A new medicine (administered as a rectal suppository) that could treat such cases of malaria is being tested in a district in northern Ghana.[1] This is part of a multi-country study sponsored by WHO in Ghana, Nigeria, Tanzania and Bangladesh. The study team in Ghana is working very closely with over 400 traditional healers to identify cases of severe malaria, provide the new medicine, and refer these cases to the nearest health facility for treatment. In all these cases the traditional healers' role is recognised and the credit for the survival of the children jointly acknowledged.[2]

Burkina Faso

In Burkina Faso a current research programme combines modern healthcare and African traditional medicine in providing treatment for people living with AIDS. Practitioners of modern healthcare are working with traditional health practitioners to assess the effects of traditional healthcare practices on patients. In one example of effective integration of traditional medicine into a modern health system, a team composed of scientists, Health Ministry officials, members of the Burkinabe Association of Traditional Health Practitioners and others, developed a protocol for the management of patients.[3]

1 The research is designed to determine the benefit of early treatment with rectal artesunate capsules.

2 The double-blind randomized clinical trial of artesunate rectal capsules on child survival in the Kassena-Nankana district Ghana, is funded by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR).

3 The Health Minister's meeting 'Integrating Traditional Medicine into Health Systems: the example of Burkina Faso' was held in Ouagadougou, Burkina Faso, from 28 August to 2 September 2000.

Combining modern healthcare and traditional medicine

3.5 Most healthcare-related research that has been externally sponsored in developing countries has not taken account of traditional medicine. In some circumstances, the belief systems of traditional healers and biomedical researchers may be so incompatible that the two groups will be unwilling or unable to collaborate in research. In other cases such collaboration is desirable, or even essential, for research to be successful. Two such examples involving malaria and HIV/AIDS are set out in Box 3.1.

Concepts of illness, disease, misfortune and death

3.6 In developing countries, sickness may become merged with general ideas of misfortune. For example, one villager may be physically sick, another emotionally distraught or suffering from a mental illness and yet another's herd of livestock may have died. All three may be regarded as suffering from the same generalised affliction, which may be diagnosed by a shaman as someone else's witchcraft or bad spirits.[1] The first two villagers' conditions may be treated by modern healthcare practitioners and indigenous herbalists as physical ailments.[2]

3.7 It is commonplace in Africa for certain ailments, especially those affecting children, to be ascribed to the effects of spirits or violations of prohibitions. Researchers may wish to avoid taking account of such explanations. Yet, these

1 A shaman is someone who is believed to mediate between the spirit world and humanity, and is able to enter into a trance or similar state and then diagnose and prescribe or effect cures for disease. The term was originally coined by scholars who were studying societies in Siberia and central Asia, and was later extended to similar religious complexes found elsewhere in the world.

2 Littlewood R (1988) From vice to madness: the semantics of naturalistic and personalistic understandings in Trinidad local medicine, **Social Science and Medicine**, 27(2) 129–48.

indigenous explanations have a kind of reality as an explanatory system of ill-health and need not be incompatible with the research. Thus, while malaria or diarrhoea are indeed often ascribed to affliction by spirits, they can also be treated as a biomedical condition.

3.8 Local people will usually accept both types of explanation as contributing to an understanding of malaria. Spirits may be invoked to explain recurrent illness (for which the traditional remedy is expulsion of the spirits causing the illness). Bad water or an infestation of mosquito larvae can be understood as explaining the immediate symptoms (with such remedies as the development and use of clean water, chemically protective mosquito nets and medicines, or clearing away undergrowth and stagnant pools around a homestead). Such conflict of ideas and explanations is structural and broadly unavoidable, and should be acknowledged and dealt with by researchers on a day-to-day basis.

3.9 Differences from Western beliefs are sufficiently widespread to affect the views of local participants in research and to influence the conduct and progress of research related to healthcare. Local researchers, even if trained in modern healthcare, are likely to be accustomed to the concepts and practices following from traditional health practices and may view them as useful. Although it is in practice difficult to assess the efficacy of such systems, biomedical researchers may wish, provisionally at least, to keep in mind a distinction between local practices which are beneficial and worth encouraging (such as passing a knife through a flame to sterilise it before cutting a newborn's umbilical cord), and those which are harmful (such as applying animal dung to the stump of the umbilical cord) and should be discouraged.[3] The use of other kinds of treatment where there is no evidence base for the assessment of useful or ill-effects may be best left to the judgement of local individuals, families and practitioners, and in some cases may be worthy of research to establish effectiveness.

3.10 Participants' beliefs about common techniques used in research, such as taking blood and urine samples, or giving injections, will also have an impact on the conduct of research. For example, sensitivity to the taking of blood samples is widespread in many parts of Africa (see Box 3.2). Some potential participants in research believe that researchers sell blood. Such individuals may resent the exercise while others may agree to provide just a very small blood sample. This might encourage researchers and field assistants to use deceptive methods to obtain larger amounts of blood if this is required by the study protocol. Providing urine samples is less unpopular and where such samples are a possible alternative to blood samples, may be preferred by study participants. There is often greater reluctance to provide samples of faeces. In part this may be because of the messy procedures for sample collection, especially as water-based sanitary facilities are often not available and the only alternative is a pit latrine. There is, however, also the belief in some areas that faeces may be used for witchcraft. In contrast to reservations about giving samples, in many developing countries injections are very popular.[4] If

BOX 3.2 Blood samples in Malawi

In Malawi there is a widespread belief that a person's blood contains his or her spirit. If blood is taken in any quantity it is feared that the spirit is also lost. Whoever takes blood is believed to control the spirit and body of the individual from whom the blood was taken. This belief does not prevent the taking of blood samples within health facilities when the individual is presumed to be sick. However, population-based studies which require blood samples are extremely difficult or impossible to conduct unless the participants are brought to a healthcare unit. As a result, taking blood samples is minimised in community-based research studies.

3 World Health Organization (1998) **Care of the umbilical cord: a review the evidence 1998 - WHO/RHTMSM/98.4**, World Health Organization, Geneva.

4 See Reeler AV (2000) Anthropological perspectives on injections: a review, **Bulletin of the World Health Organization**, 78(1) 135–43.

such belief systems are to be taken into account when research is designed, researchers will require knowledge of, or access to those with knowledge of, the languages and concepts used in discussions and practices of healthcare.

The doctor–patient relationship; the healer–client relationship

3.11 It cannot be assumed that there is only one model of doctor–patient or healer–client relationship. This applies not just across the spectrum of medical systems but also within healthcare systems. An early Western model of the doctor–patient relationship saw it as essentially harmonious and based on the patient's unquestioning acceptance of the doctor's superior status and skills.[5] A later model proposed an inherent conflict between doctor and patient deriving from the difference in power between the two, a difference which in some cases has to be negotiated and which may therefore not be harmonious.[6]

3.12 A similar range of possible doctor–patient relationships is likely to be found in different cultures. One report from Pakistan refers to traditional Muslim healers (called *pir*) who are regarded as imbued with God's power and so never need to make diagnoses: just seeing the patient will allow them to know the patient's condition and prognosis.[7] Reports from Africa suggest much more negotiability between doctor and patient, with the latter entitled to argue with the doctor or healer over the diagnosis and possible cure.[8] In between are the more complicated variations, for example in which healers physically identify or empathise with patients, by co-ordinating their pulse rates with those of the patient and then using this common point of identification for diagnosis and cure.[9]

3.13 Researchers from developed countries may not be fully aware of prospective participants' considerable trust in and respect for medical doctors and other healthcare practitioners, even those with modest qualifications. This may be especially true if the healthcare practitioners have been trained in Western countries. It is questionable whether researchers from developed countries are well prepared for the enormous responsibility that this attitude of respect and trust places upon them. The implications of this attitude for the consent process are discussed in paragraph 6.24.

3.14 In many instances researchers from developed and developing countries may have more in common with their counterparts from other countries than they do with the population under study in rural or less-educated areas. Discussion with interpreters, cultural assistants, indigenous healers and shamans will provide researchers with a means of understanding some of the religious and cultural issues that may have a bearing on research related to healthcare. Such cultural understandings are especially important if the researchers are principally male and the interpreters and cultural assistants are predominantly female. Similarly, gender differences among local practitioners may be significant: for instance, in some societies, traditional herbalists

5 Parsons T (1964) **Social structure and personality**, Free Press of Glencoe, New York; Collier-Macmillan, London.

6 Hahn RA and Gaines AD (eds) (1985) **Physicians of Western medicine: anthropological approaches to theory and practice**, Reidel, Doordrecht. Kleinman AK (ed) (1980) **Patients and healers in the context of culture. An exploration of the border-land between anthropology, medicine and psychiatry**, University of California Press, Berkeley.

7 Ewing KP (1984) The Sufi as saint, curer and exorcist in modern Pakistan. In Daniel EV and Pugy JF (eds) **Contributions to Asian Studies**, EJ Brill, Leiden, Netherlands.

8 Davis-Roberts C (1981) Kutambuwa ugonjuwa: concepts of illness and transformation among the Tabwa of Zaire, **Social Science and Medicine**, 15(3) 309–16.

9 Daniel EV (1991) The pulse as icon in Siddha medicine. In Howes D (ed). The varieties of sensory experience, **A Sourcebook in the Anthropology of the Senses**, University of Toronto Press, Toronto. Hsu E (2000) Towards a science of touch, Part 1: Chinese pulse diagnostics in early modern Europe, **Anthropology and Medicine**, 7(2) 251–68. Hsu E (2000) Towards a science of touch, part II: representations of the tactile experience of the seven Chinese pulses indicating danger of death in early modern Europe, **Anthropology and Medicine**, 7(3) 319–33.

are male and shamans female. Differences in interpretation as a result of gender may need to be taken into account in planning local participation in research and understanding of research as carried out in developed countries.

3.15 In addition, there may be a tension between participants' respect for those with training in developed countries, education and knowledge and their respect for traditional figures of wisdom and authority, including leaders of the community. Elders in the community commonly occupy positions of trust and may be respected for their local knowledge: differing circumstances of particular situations may determine which kind of knowledge is preferred, and by whom. For example, differing views as to where pregnant woman should have their confinements were observed in rural coastal Kenya before the advent of AIDS. Some of the older men preferred pregnant women to have their confinements at home attended to by a traditional midwife.[10] A number of them thought hospital confinements were an unnecessary expense, as they considered the traditional method to be successful. In contrast, almost all the pregnant women wanted to give birth at a local mission hospital, with family members in attendance.[11] However pregnant women also often turned to older members of the homestead for healing and dietary advice.

Informing prospective participants about research

3.16 In many developing countries, concepts of respect for the family and community are equally as important as, or more important than, concepts of individual autonomy and rights. The belief that there may be mutual effects on each other by members of a kinship or other group is found in many non-Western societies. For example, in parts of Africa, if one person commits an offence, such as the violation of a sexual prohibition, the whole village or family may have to undergo a cleansing ritual in order to rid themselves of the harmful effects of that person's act.[12] This is a quite different understanding of individual autonomy from that found in many developed countries. In such circumstances, to seek individual consent without first creating public or group acceptance is likely to cause conflict within a community.

3.17 Often public discussion, followed by consultation with family units including women members, appears the most feasible and productive course to inform prospective participants about research, although variations in the cultural context will shape the manner in which this can be done. Without doubt it is often a slow process, requiring knowledge not only of the local political structure, language and relevant idioms but also of the customs defining behavioural etiquette and local moral systems (see Box 3.3). Community discussion and acceptance are also perceived as valuable and integral parts of promoting respect for persons and the dignity of individuals in developed countries.

Decisions about research

3.18 In some districts of developing countries, decisions about an appropriate course of action are made within a hierarchy of customary roles in the family and community. Men are most often in

10 Parkin D (2001) Personal communication, University of Oxford.

11 This preference appeared to be based on two factors: young women's claims, based on observation, that hospital births were more successful than homestead ones; and a wish to avoid the traditional midwife's method of inducing slow birth by forcing the infant out through externally-applied pressure.

12 See, for example Turner VW (1968) **The Drums of Affliction: a study of religious processes among the Ndembu of Zambia**, Oxford University Press, Oxford.

BOX 3.3 Discussing research: China

Government policy in mainland China has imposed a degree of uniformity in the structure of rural villages, where public discussion is the most likely forum in which the objectives of research can be communicated to members of a village. Villages below the level of townships tend to be self-governing collective units, organised by elected village cadres, some of whom are government party members. It is, for instance, through these cadres that information and monitoring with regard to the one-child family policy is carried out. Although imperfect, there is thus in principle a well-established official medium for the public discussion of research related to healthcare, its objectives and the need for local participants. Provided that the cadres in China accept the value and feasibility of a research project, would-be participants can choose whether or not to consent to participate in research. Moreover, with the possible exception of some remote areas, it is unlikely in modern China that women are expected to obtain the permission of men or elders before agreeing to be involved in research. Nevertheless, before consent can be sought, a visiting research team's proposals will need to be discussed in an open manner through the offices of the village cadre committees.[1]

1 Pieke F (1996) **The Ordinary and the Extraordinary: an anthropological study of Chinese reform and the 1989 People's Movement in Beijing**, Kegan Paul International, London and New York. Hsu E (1999) **The Transmission of Chinese Medicine**, Cambridge University Press, Cambridge.

charge of such decision-making about participation in research by virtue of their status as head of the household or community (see Box 3.4). In addition mothers-in-law commonly exert power over daughters-in-law in some South Asian regions. Women, particularly young women, may not therefore always be able to express personal opinions on even minor matters, let alone the issue of whether they would like to take part in research. The notion that individuals are free to make their own decisions will therefore be less familiar to such women. The role of researchers in such circumstances is discussed in Chapter 6. Given that mortality and morbidity in both children and women are unacceptably high in many developing countries, research relating to child and reproductive health remains a priority. In a social context where women and children are vulnerable, they may be excluded from participating in research that is likely to benefit them or, conversely, exploited for research purposes precisely because they are vulnerable.

3.19 Attitudes have changed dramatically in much of Africa, where many women, especially in non-Muslim societies, have now cultivated a more assertive position with regard to healthcare, often aided by mission hospitals, clinics and health-focused non-governmental organisations (NGOs) (see Box 3.5). The rapid and increasing emergence of households

BOX 3.4 Consent to research: Uganda

In some areas of Uganda that hold to traditional social and cultural values, the head of the immediate family is a man (husband/father) and it is widely recognised and expected that he takes the final decision on all matters, especially sensitive ones affecting family members. In these areas, family members who do not submit to such decisions may face serious consequences including domestic violence and/or divorce. Thus, in such circumstances women and children will tend not to participate in a study unless permission has been granted by the head of the household. However the Ugandan guidelines require investigators to obtain 'the legally effective informed consent of the individual research participant'. In addition they explicitly state that 'a community leader may not consent to the participation of community members'.[1]

1 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda: 32.

headed by women in parts of Africa as a result of AIDS may have accelerated these changes in attitude. As cultures are not fixed, researchers may need to find means of fostering discussion about what is required by cultural norms in a particular context. For example, research in South Africa has shown that even within a culture with strong beliefs about the importance of the community, many women favour the approach of requiring individual consent to research.[13] The issue of cultural sensitivity is discussed further in Chapters 4 and 6.

3.20 In contrast to the examples above, in Latin America, substitute consent, community consent or other types of group or corporate consent are usually not practised. Although collective information can be given to rural communities or ethnic minorities, such as indigenous populations, consent by individual participants has been the rule. In research into vaccines in Colombia involving the military population, consent was initially sought at the command level and then at the individual level, before participants were enrolled. Although the trial was fully supported by the military command, a large proportion of volunteers felt able to choose to withdraw from the vaccination scheme before the second and third doses due to a range of side-effects.[14]

BOX 3.5 Consent to research: Ghana

In a study in northern Ghana to determine culturally appropriate models of health and family planning services for the population, a district-wide experiment was established to document the impact of health and family services on child mortality and fertility.[1] The community participated actively in the development of the experiment and approved its design. A key feature of the research was the provision of modern family planning services to men and women in this rural population, where they had previously not been available. The men insisted on being consulted before their wives were offered family planning services. However, the women, with the assistance of the research team, organised several community meetings to discuss the implications of consent in the male-dominated society. After several public meetings where the issue was openly debated between the men and women, the women succeeded in convincing the men to accept that the women could use the family planning services either with dual consent of the couple or with the consent of the woman alone. The research team also agreed that information on consent would be treated as confidential.

1 Binka FN, Nazzar A and Phillips JF (1995) The Navrongo community health and family planning project, **Studies in Family Planning**, 26(3) 121–39; Nazzar A, Adongo PB, Binka FN, Phillips JF and Debpuur C (1995) Developing a culturally appropriate family planning program for the Navrongo Experiment, **Studies in Family Planning**, 26(6) 307–324.

3.21 As in developed countries, in developing countries there may be a variety of reasons why people are willing to participate in research projects. Participants may be motivated by self-interest, in particular by the belief that a research project may provide them with a new and effective treatment for their illness. Alternatively, participants may consent to take part in research because it provides their only opportunity to receive adequate healthcare. In the case of HIV-positive participants in research in Thailand, a primary motivation to participate was the provision of an effective treatment for their condition (see Box 6.5). Participants may also be motivated by altruistic beliefs about the power of the research to benefit their community, whether that community is defined in geographical terms, or in terms of the community of people with a particular disease. Research in Chile has shown that, for some women, participation in research was a valued opportunity to 'contribute to all women's health', or 'to a better future'.[15]

13 Lindegger G (2002) Culture and informed consent in clinical trials in South Africa, Third Global Forum on Bioethics in Research, Capetown, South Africa, 21–23 February 2002.

14 Velez ID, del Pilar Agudelo S, Arbelaez MP, Gilchrist K, Robledo SM, Puerta JA *et al* (2000) Safety and immunogenicity of a killed Leishmania (L.) amazonensis vaccine against cutaneous leishmaniasis in Colombia: a randomized controlled trial, **Transcripts of the Royal Society of Tropical Medicine and Hygiene**, 94(6) 698–703.

15 Sanchez S, Salazar G, Tijero M and Diaz S (2001) Informed consent procedures: responsibilities of researchers in developing countries, **Bioethics**, 15(S16) 398–412.

3.22 Prospective participants in developing countries place high value on healthcare. Consequently it is often assumed that they may be more likely to participate in research related to healthcare, although this is not easy to demonstrate. In addition, a lack of familiarity with the methods and rationale of research related to healthcare, may lead participants to believe that the primary purpose of research is to provide them with therapy, rather than to obtain information (commonly called 'therapeutic misconception'). The US National Bioethics Advisory Committee (NBAC) recommended that investigators working overseas must indicate in their research protocols how they intend to minimise the possibility of therapeutic misconception.[16] We conclude that investigators conducting studies in developing communities have a special responsibility to explain to those participating in research that the research may not benefit them as individuals so that they do not participate in the false expectation of gaining a direct benefit. In areas where physicians are thought of solely as healthcare providers, and where research is a novel concept, particular care must be taken. Issues relating to consent are discussed in more detail in Chapter 6.

16 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**: Recommendation 3.10.

Chapter 4

The ethical framework

Introduction

4.1 In Chapter 2 we noted the wide variations in the health of populations around the world. These variations exist in a context of considerable interdependence between countries, not least with regard to international trade. Scientific research and research related to healthcare are themselves international enterprises, the findings of which may transcend national and political borders. Commercial enterprises, including pharmaceutical companies, seek to take legitimate advantage of the economies of scale that global markets offer. The economies, social systems and politics of countries are thus bound together in complex ways.

4.2 As well as considerable variations in health of populations, there are also wide variations in the ability of different countries to cope with the problems which they confront. These differences of capacity stem largely from varying economic resources, but also relate to variations in administrative and political capacity and the differential development of expertise in scientific and technical disciplines in the world. Moreover, as discussed in Chapter 2, it is often the case that those countries with the greatest health needs are also those with the least capacity to deal with them. For example, some of the highest rates of HIV infection are in countries that are among the poorest of the world. In situations of poverty, with very limited scientific, administrative and political capacity, as well as economic inequalities, individuals and organisations face major difficulties in delivering the healthcare needed.

4.3 Many interpretations can be, and have been, offered for this pattern of global inequality. One view is that it is a legacy of colonialism and empire. Built upon a basis of economic exploitation, newly de-colonised nations in the middle of the twentieth century were left with inadequate political and social institutions with which to face the challenges of economic and social development. Another view is that the pattern of global inequality represents a series of structural barriers raised against the poor, making it extremely difficult, if not impossible, for them to develop an economic basis sufficient to sustain a reasonable standard of life for their citizens. A third view is that, despite the history of colonialism, the modern international order does offer opportunities for economic growth, provided that poorer countries have the appropriate policies and institutions in place to take advantage of their comparatively low costs to compete against established economic powers.

4.4 In this Report, we do not take a position on these competing interpretations. We simply acknowledge the difficulties confronting those seeking to improve the health of populations in developing societies, and we accept that the barriers to sustainable development are considerable. Yet within these constraints, individuals and corporate bodies still have choices. The moral burden of choice weighs especially heavily on those who enjoy a privileged position in the world order because, by definition, they have the greatest capacity to effect change, but it also applies more widely. In particular, the problem is raised of how to devise an approach to research related to healthcare that is consistent with the requirements of an ethical framework for research.

4.5 What do we mean when we speak about an ethical framework for research? We have in mind a set of principles that allow us to evaluate the actions and policies of individuals and bodies such as companies, non-governmental organisations (NGOs), international organisations or government agencies. These principles seek to identify the considerations that should apply to individuals and agencies when they make decisions or adopt policies. They constitute a framework for articulating the duties, obligations, claims and expectations of those involved in research related to healthcare.

4.6 We do not present these principles as part of a more general ethical theory. This does not mean that the principles are drawn from nowhere: they are widely discussed in works on ethics and

political theory. We offer them as the basic considerations which anyone concerned to reflect upon and evaluate research related to healthcare in developing countries should take into account. We consider four principles in particular:

(i) the duty to alleviate suffering

(ii) the duty to show respect for persons

(iii) the duty to be sensitive to cultural differences and

(iv) the duty not to exploit the vulnerable.

The task of the Working Party was to consider how these principles should be understood in the context of research related to healthcare in developing countries and of the particular dilemmas that arise, while taking account of the practical, social, cultural and economic circumstances that are relevant to research.

The duty to alleviate suffering

4.7 Medical practice is fundamentally justified by the duty to alleviate suffering. This duty has long been acknowledged in moral codes and its application to medicine is enshrined in the Hippocratic Oath. It is commonly argued, and recognised in most political structures, that the needs of one's own communities should have first claim on this duty and thus on the resources available. But this does not mean that we have no duty to contribute to the alleviation of suffering elsewhere, especially among the citizens of poor countries.

4.8 Since medical research, and research related to healthcare generally, make an essential contribution to the alleviation of suffering, the conduct of research which deals with the health problems in developing countries is not just legitimate, it is a moral duty. For most people, the duty to conduct research addressed to the needs of developing countries is discharged only indirectly, by government support for publicly-funded institutions such as the Medical Research Council (MRC) in the UK and the National Institutes for Health (NIH) in the US, the Framework Programmes of the European Union and the many national aid agencies in developed countries (see Box 2.2). Nonetheless, it matters morally to all of us that effective medical research and research related to healthcare is indeed carried out. There is an inescapable moral duty which must be the basis for public policy in this area.[1]

4.9 The duty to alleviate suffering enjoins us to do what we can to reduce the amount of suffering in the world. Thus we fail to act in accordance with this duty by doing nothing to help eliminate avoidable suffering; and the more suffering we help to eliminate, the better our action. But there are many other claims on our time and resources, and acknowledging the fundamental status of the duty to alleviate suffering does not mean that it always overrides all other claims. Instead, there is a difficult task for individuals and, especially, governments to strike an acceptable balance between competing demands. It is not part of this Report to propose a method for undertaking this task. But the fact that externally-sponsored research related to healthcare may be undertaken in a context in which resources are limited has important implications for its conduct. This is one aspect of the issues about standards of care discussed in Chapter 7.

1 Furthermore, this research is increasingly also a matter of enlightened self-interest, since immigrants from developing countries, and travellers to them, may bring some of the health problems of the developing world back to the developed world.

Respect for persons

4.10 The duty to alleviate suffering focuses on just one human quality, the capacity for suffering. But humans share many characteristics. As well as having common basic needs they also have the capacity to think, reason, use language and live in complex relationships with one another, thereby creating their own cultures and allowing individuals the opportunity to pursue their own projects within these cultures. This capacity for creating a life of our own is both an essential feature of common humanity and yet also something that marks out each of us as a unique source of value. It justifies the requirement that we regard each other as worthy of respect.

4.11 In holding every person worthy of respect, we commit ourselves to taking their interests into account when considering what to do. We may not use them as a mere means either to our own ends or to the welfare of others, and, on the presumption that they are the best guardians of their own interests, they should be involved in decisions which affect them. Hence, among other things we should not increase their risk of illness or death, misinform them, violate the integrity of their intimate relationships, or treat with indifference what they deeply value. Positively, we should support their sense of self-respect and self-worth, encourage them to develop and express their capacities, and help create conditions in which they can lead worthy and meaningful lives.

4.12 Understood in this way, the duty of respect for persons places important constraints on the implementation of the duty to alleviate suffering. That duty, by itself, may lead to the assumption that the less suffering there is, the better. However, the principle of respect enjoins us to consider carefully the ways in which we seek to alleviate suffering. For example, policies which violate other interests of those involved, even if they offer the most straightforward way of reducing suffering, are to be weighed carefully. Equally, issues related to balancing the interests of participants in research with the interests of the wider population who could benefit from the research results are addressed in Chapter 7.

Sensitivity to cultural differences

4.13 An important characteristic of externally-sponsored research carried out in developing countries is that there are often cultural differences between those organising or funding the research and the research workers and participants in the host country (see Chapter 3). The moral significance of these differences requires special attention.

4.14 Individuals live within particular societies, the cultural assumptions and practices of which shape their understanding of themselves and others. The ways in which different peoples define themselves in terms of gender, family, kinship, status and nation, and go on to organise relationships involving matters of authority and questions of sickness and health, are endlessly varied. Even when they are in revolt against their cultural upbringing, individuals often tend to think of themselves in the light of the concepts and understandings they have acquired in their society, including their understanding of sickness and health.

4.15 As a result, the general duty of respect implies a duty to be sensitive to other cultures. Thus one potential misuse of power is to be insensitive to the cultural perspectives that individuals bring to questions of health and healthcare. Indeed, the variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. This in turn prompts an analysis of the relationship between the requirement of sensitivity to cultural differences and the concept of moral relativism, the view that different moral codes cannot be critically compared and evaluated.

4.16 In our view, recognition of the existence of diverse cultures and communities with different moral codes does not lead to moral relativism. The relativist position mistakenly suggests that because

a particular set of moral norms is embedded in the culture, it must be accepted uncritically. This is to confuse two distinct questions:

(i) What does the local culture prescribe?

(ii) What is the right thing to do bearing in mind the local culture?

Ethical judgements are of this second type. Thus, sensitivity to the values inherent in local practices does not require uncritical acceptance of them.

4.17 What then are the demands placed on us by the requirement of sensitivity to cultural differences? Plainly, one demand is the willingness to explore such differences without prejudice and to seek as far as possible to understand them informed by knowledge of local traditions and material circumstances. Equally, once this understanding has been achieved, those organising research related to healthcare should as far as possible take account of the local culture, taking the trouble to find ways that respect local practices even where, on the face of it, they complicate the research. But, it does not require those involved to compromise fundamental values. In particular, since sensitivity to cultural differences is an implication of the fundamental principle of respect for persons, if local cultures transgress values inherent in this principle, researchers will need to follow different procedures from those prescribed in the local culture.

4.18 This analysis is particularly relevant when we consider the need for consent by participants in clinical trials. One of the distinguishing characteristics of cultures in developing societies is that they are often less individualistic than those in Western Europe and North America. In such cultures, consent may not be seen to be a purely individual matter. It may be associated with wider obligations to family, village or clan (see paragraph 3.18). Our approach in this chapter suggests that when we come to consider the requirements for consent in Chapter 6, we need to be sensitive both to local cultural traditions and to the general requirement of respect for persons implied by our common humanity.

The duty not to exploit the vulnerable

4.19 We have already stressed that the context of our Report is one in which there are considerable inequalities of power and advantage between developed and developing countries. We suggest that, as a matter of moral principle, the more powerful have a duty to refrain from exploiting to their own advantage the vulnerability of the weaker. Since those with power may always be tempted to misuse it, perhaps even for what they perceive as benevolent reasons, it is important to insist on this principle.[2] We have a number of points to make about the principle.

4.20 First, it can be regarded as a further implication of the principle of respect for persons, for in exploiting others we fail to give proper weight to their interests. Secondly, like the requirement of sensitivity to cultural differences, the duty not to exploit the vulnerable merits special attention in the context of developing countries, not least because outsiders and local citizens may well differ on just what counts as exploiting or taking advantage of the weakness of others. Thirdly, it is important that the duty not to exploit the vulnerable be observed uniformly by all individuals and organisations involved in research, to avoid unfairness and the danger of undermining the principle in practice. If only some sponsors act in accordance with the principle of non-exploitation, then such scrupulous sponsors would be disadvantaged in relation to unscrupulous sponsors. Fourthly, although the duty not to exploit the vulnerabilities of others falls on all, the

2 For a general discussion of the importance of protecting the vulnerable as a matter of social responsibility, see Goodin RE (1985) **Protecting the Vulnerable**, University of Chicago Press, Chicago.

nature of the obligation may change depending on who is involved. For example, those occupying positions as policy-makers in political and social organisations at national or international levels have an obligation not simply to provide for the avoidance of exploitation within the framework of existing practices and institutions, but also to pursue change in the functioning of those institutions and practices so as systematically to reduce the opportunities for exploitation.

4.21 Hence, the principle of not exploiting the vulnerable does not mean that we simply take the current context of research related to healthcare in the developing world as unchallengeable and unalterable. Just as it is unacceptable that local political and economic elites should seek to pursue their own goals at the expense of populations participating in research, it is unacceptable that researchers should select populations which are economically or politically weak, and therefore vulnerable to exploitation, in order to test therapies more cheaply in order to benefit other, wealthier communities. The wider roles and obligations of all those involved in research, pharmaceutical companies, international organisations, governments, and individuals in reducing global health inequities must always be borne in mind. In particular, in the context of research, researchers have a duty to enable the participant communities in developing countries to benefit, where possible, from the research conducted on them. This point, along with the broader question of developing expertise in research, is a matter to which we return in Chapter 9.

From principle to practice

4.22 We have discussed four interrelated ethical principles relevant to the conduct of research in developing countries. They should not be thought of as rules to be applied mechanistically. By their very nature, they call for interpretation and consequently for the exercise of judgement, especially in relation to the latter two principles concerning sensitivity to cultural differences and the avoidance of exploitation. The importance of some cultural difference may not be clear initially, nor may it be clear at what point the standard of care extended to participants in research becomes exploitative. Thus, when considering how research related to healthcare should be conducted, it is important to analyse how such judgements are to be made, appraised and implemented. Principles must be translated into practice, and for this a proper procedure must exist. The analysis of such procedures is an important part of our discussion. There need to be suitably informed and accountable bodies in both the country in which the research is sponsored and the country in which it is carried out to take responsibility for striking a proper balance between the various conflicting considerations which arise. In Chapter 8 we discuss the way in which research ethics committees can play this role.

4.23 We emphasise one point here: the establishment and maintenance of research ethics committees is just as much an essential ingredient in the proper conduct of research related to healthcare as the functioning of political institutions is essential to the proper conduct of government. An ethical analysis does not concern itself only with identifying and setting out appropriate general values and principles. It also has to concern itself with the institutions and procedures through which these principles are put into practice.

Chapter 5

The framework of guidance

Introduction

5.1 The conduct of research related to healthcare is subject to a wide range of national and international guidance, guidelines, declarations and regulations (which we will call guidance, except for those regulations which have the force of law). The international guidance has formed the basis for the national guidance adopted in many countries. In general, the guidance covers a wide range of activities in research involving human participants. In Chapter 4, we set out four principles that should guide decision-making in the conduct of research related to healthcare in developing countries, which is sponsored by other, developed countries: the duty to alleviate suffering, the duty to show respect for persons, the duty to be sensitive to cultural differences, and the duty not to exploit the vulnerable. These principles are reflected in the various forms of guidance but are sometimes expressed in different ways. For example, respect for persons is sometimes expressed more narrowly as respect for individual autonomy. The duty to alleviate suffering is sometimes referred to in terms of beneficence, or a duty to benefit other people, and the duty not to exploit the vulnerable encompasses guidance expressed in terms of fairness and justice.

5.2 In addition, two common themes arise in the various forms of guidance. The first is the need for research to be based on sound scientific principles, on knowledge derived from laboratory and animal experiments, if appropriate, and on a sound understanding of the scientific literature. The second is the need to ensure that the results of research are accurately reported and published, that publication can only take place where it can be demonstrated that ethical principles relevant to the conduct of research have been observed, and that negative as well as positive results are reported.

5.3 Over recent years, there has been increasing criticism of much of the guidance which exists on two counts. First, while such guidance sets out the fundamental ethical principles relevant to the conduct of clinical research on human participants, it is too general in nature to address many of the specific and often controversial issues that are raised by such research. For example, guidance about the standards of care which should be used in clinical trials and the availability of treatment after a trial is over is set out in very general terms and has been subject to varying interpretations.[1]

5.4 Secondly, the various forms of guidance, whether international or national, in many instances do not take into account the special circumstances that attend research undertaken in developing countries and sponsored by developed countries. In addition developing countries often have little or no relevant national guidance. In such situations, where research is externally sponsored, there is a danger that the conduct of the research may fail to reflect the cultural and social values of those from the developing countries who participate. In this chapter, we review the broad framework of guidance which concerns research related to healthcare and consider how the specific issues raised by externally-sponsored research are addressed.

The historical context

5.5 During the last century, there have been a number of notorious cases in which participants have been harmed as a consequence of unethical clinical research. The Nuremberg Code was formulated in 1947 following the Nuremberg trials, at which a number of Nazi researchers were convicted. The trials revealed that research on human beings had been conducted by Nazi physicians in Germany without due regard to the welfare or, indeed, the survival of the

1 In the debate concerning the 'standard of care' in the perinatal HIV transmission studies (see Box 1.2), both sides cited the CIOMS 1993 guidelines to support their position. Debate centred on the question of whether the 'best proven diagnostic and therapeutic method' (Article II:3 of the 1996 Declaration of Helsinki) should take local resource considerations into account.

participants. The central feature of the Nuremberg Code was the protection of the integrity of the person participating in research. The Nuremberg Code was endorsed by the World Medical Association (WMA), which published the Declaration of Helsinki in 1964. The Declaration, which has been revised five times to date (Table 5.1 and Appendix 1), sets out the principles to be observed in research on human participants and has become the cornerstone of research related to healthcare. Its standing is such that the principles enshrined in it have been incorporated into many of the forms of guidance that have subsequently been drawn up to govern the conduct of research related to healthcare (see Table 5.1 for international guidance and Appendix 1, Table 1 for national guidance).

Table 5.1

International guidance for the conduct of research related to healthcare

Year	Organisation	Title
1947	War crimes tribunal at Nuremberg	Nuremberg Code
1948	United Nations General Assembly	Universal Declaration of Human Rights
1964	World Medical Association (WMA)	Declaration of Helsinki (1)
1975	WMA	Declaration of Helsinki (2) Tokyo
1983	WMA	Declaration of Helsinki (3) Venice
1989	WMA	Declaration of Helsinki (4) Hong Kong
1991	CIOMS/WHO	International Guidelines for Ethical Review of Epidemiological Studies
1993	CIOMS/WHO	International Ethical Guidelines for Biomedical Research Involving Human Subjects (Under revision in 2001–2)
1995	WHO	Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products
1996	WMA	Declaration of Helsinki (5) South Africa
1996	International Conference on Harmonisation (ICH)	Harmonised Tripartite Guideline. Guideline for Good Clinical Practice
1997	Council of Europe	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine
1997	UNESCO	Universal Declaration on the Human Genome and Human Rights
2000	European Union	Charter of Fundamental Rights of the European Union
2000	UNAIDS	Ethical Considerations in HIV Preventive Vaccine Research
2000	WHO	Operational Guidelines for Ethics Committees that Review Biomedical Research
2000	WMA	Declaration of Helsinki (6) Edinburgh
2001	European Parliament and Council of the European Union	Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

International guidance for the conduct of research

5.6 The potential risk of harm to participants in research related to healthcare has led to widespread agreement that rigorous safeguards should be established irrespective of the geographic and economic setting in which it is undertaken. The present regime of guidance has developed largely in response to problems that have been encountered during the evolution of research related to healthcare. The major sources of international guidance have undergone, or are in the process of undergoing, revisions and development, but these revisions have generally been initiated to address specific shortcomings.

5.7 The implementation of guidance is the responsibility of those who are in contact with, or responsible for, participants in research. They will include government officials, aid agencies, institutional researchers, administrators and researchers, public and private sponsors of research, the senior management of companies, and research ethics committees. Ultimately, responsibility for observing and applying the guidance falls to those actively engaged in carrying out research involving human participants in the clinic, ward, laboratory or elsewhere. It is therefore important that guidance is written in terms which encourage consistent interpretation and which can be applied with confidence.

5.8 The guidance ranges from guidelines which claim general applicability, such as the Declaration of Helsinki and the guidelines of the Council for International Organizations of Medical Sciences (CIOMS)[2] to those with more narrow remits such as those set out in the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use** (ICH) which apply to the pharmaceutical industry, or **Ethical Considerations in HIV Preventive Vaccine Research** published by UNAIDS, which apply specifically to research into vaccines for a single disease (HIV/AIDS). In the next two sections, we consider how the Declaration of Helsinki and the CIOMS Guidelines apply in the context of research sponsored by developed countries and conducted in developing countries.

The Declaration of Helsinki

5.9 When the Declaration of Helsinki was published in 1964, the scope of its provisions was considered to be comprehensive. The Declaration established a set of basic principles from which were derived some general rules of conduct. The current revision (2000) recognises that the purpose of biomedical research involving human participants must be to 'improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease' and further, that medical progress is based on research that must at some stage involve human participants (see Box 5.1).

5.10 According to the current version (2000) of the Declaration, any research carried out involving human participants must be based upon sound scientific principles, and according to a properly formulated protocol for the study that has been subjected to the scrutiny and advice of an independent committee (i.e. a research ethics committee). The Declaration recognises the fact that most interventions – diagnostic, therapeutic and preventative – and especially those involving biomedical research, involve hazards and that the issues of risk and hazard must be addressed. It notes that when research involves healthy volunteers, special care must be taken to determine if the objective of the research outweighs the inherent risks and burdens to participants. The Declaration pays particular attention to the problems that may arise where research is combined

2 The guidelines were developed in collaboration with WHO.

BOX 5.1 Revisions to the Declaration of Helsinki

The Declaration of Helsinki has been revised five times by the WMA since its initial adoption in 1964. The revision in 1996 was accompanied by considerable debate and within a year, the American Medical Association (AMA) had proposed another significant revision. In addition to including a consideration of research in developing countries, the draft revision amended or expanded guidance relating to consent and review of the ethics of research, the involvement of pregnant women in research, possible conflicts of interest, data and confidentiality, and the publication of research results.

As the Declaration is considered to be the pre-eminent guidance on ethical principles in research relating to healthcare, there was criticism of the process for such a substantial revision of the Declaration, which had been restricted to members of the WMA. In response to this criticism, the draft revision proposed by the AMA was circulated for public comment. Concerns were expressed that a number of protections for participants in research were being minimised or removed. These included provisions relating to the standards of care provided to participants in research, responsibility for participants in research and publication of research results.[1] Those in favour of substantial revision argued that these provisions and others were not relevant to a number of situations in research, and were frequently breached. It was proposed that the guidance be updated so that it took greater account of current practice. A counter-argument was that it was the current practice that was unethical and the guidance needed only minor revision. Rather than substantially rewriting the fundamental guidance relating to research related to healthcare, it was claimed that the Declaration should continue to evolve slowly, with minimal amendments, and focus on setting out fundamental principles, about which there was broad agreement. Guidance about the application of principles could then be provided in accompanying commentaries, which could be updated more frequently.[2]

The revision proposed by the AMA was rejected and the WMA charged a committee with the task of putting together a new draft. This was circulated for comment, and adopted as a revision to the Declaration at the WMA meeting in Edinburgh in 2000. It was greeted with approval from critics of the AMA draft.[3] However, a number of organisations have since claimed that paragraph 29 (concerning standards of care provided to participants in research) and paragraph 30 (concerning what happens once research is over) of the revised Declaration are inappropriate. The WMA has recently published a note of clarification for paragraph 29 (Table 5.2).

1 Anon (1999) Helsinki Declaration revising continues, **Bulletin of Medical Ethics**, 146 3–5.
2 Review (1999) Revising the Declaration of Helsinki: a fresh start, **Bulletin of Medical Ethics**, 151 13–17.
3 For example, commentators from Public Citizen asserted that the revised Declaration meant that 'researchers [would now] have no choice but to provide scientifically proven interventions-regardless of where the research is conducted' (see letter to the editor, **Washington Post**, 17 October 2000).

with professional care. Whilst a physician can combine medical research with clinical care (see Box 5.2), this is only justified by the potential benefits which may accrue for the patient and the group to which he or she belongs and subject to special provisions, including an assessment of the benefits, hazards and discomforts of the new procedure along with a comparison with the advantages of the best current methods, if such exist.[3]

5.11 The Declaration states that the hazards attendant upon the project must be predictable and where they outweigh the potential benefits, the research should not proceed. In carrying out such an assessment, the interests of the subject must always prevail over the interests of science, industry, or society. Furthermore, the Declaration states that participants always have the right to safeguard their integrity and their privacy. The importance of these considerations is that they lead on to the central requirement: that before research related to healthcare can be carried out involving human participants, the participants must first be adequately informed about all relevant aspects of the study including its aims, procedures, attendant risks and hazards and the potential

3 World Medical Association (2000) **Declaration of Helsinki**: paragraphs 28–29 (see Appendix 1).

benefits and discomforts, and then their consent sought. Informed consent must be freely given by the participants. The issue of consent is discussed in Chapter 6.

5.12 As noted in Chapter 1, there has been a major debate over whether the standard of care provided to participants in one specific form of research, the clinical trial,[4] in a developing country should always involve that diagnostic, prophylactic or therapeutic method which has been proved to be the best. Such methods may be beyond the means of those in the developing country. In such a case, it has been argued that it is acceptable to conduct research on new treatments by comparing them with alternative treatments or placebo rather than the best treatment. The current revision of the Declaration states that 'The benefits, risks, burdens and effectiveness of a new method [of treatment] should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods' (paragraph 29). This does not, of course, exclude the use of placebo, or of no treatment, in studies where no proven prophylactic, diagnostic or therapeutic methods exists. But, it appears to stipulate that the best treatment be made available by way of comparison to all other circumstances. Following concerns that paragraph 29 could not be implemented in developing countries, the World Medical Association published a 'clarification note' in 2001. The note states that in general placebo-controlled trials should only be used in the absence of existing, proven therapy. However two exceptions are outlined:

- where for compelling and scientifically sound methodological reasons [the use of placebo-controlled trials] is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any addtional risk of serious or irreversible harm (see Appendix 1).

This issue is discussed in depth in Chapter 7.

5.13 The question of what care a participant should receive once research (combined with medical care) is over has also proved controversial. Guidance on this point was included in the current version (2000) of the Declaration of Helsinki for the first time. Paragraph 19 of the Declaration states that 'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.' Paragraph 30 states that 'At the conclusion of the study, every patient entered into the study should be

BOX 5.2 Distinguishing between therapeutic and non-therapeutic research

The practice of distinguishing between therapeutic and non-therapeutic research[1] has now largely been abandoned because of a growing recognition that most trials involving therapeutic research contain non-therapeutic components and we have therefore not attempted to make such a distinction in the Report.[2] In the following chapters, much of the discussion focuses on research that contains a therapeutic component (see especially Chapters 7 and 9). However, the discussion of principles underlying research, and in some cases the conclusions and recommendations (particularly in Chapters 6 and 8) are also relevant to research without a therapeutic component.

1 We use the term 'therapeutic research' to indicate research having the potential to produce a real and direct benefit for the participants and 'non-therapeutic research' to mean research without such potential.

2 Nuffield Council on Bioethics (1999) **The ethics of clinical research in developing countries**, Nuffield Council on Bioethics, London.

4 See the glossary for a definition of clinical research and clinical trials.

assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' We give detailed consideration to this issue in Chapter 9.

The CIOMS guidelines

5.14 CIOMS, in collaboration with WHO, recognised the special circumstances which arise when applying the Declaration of Helsinki to research undertaken in developing countries, and proposed guidelines to address them in 1982. These guidelines sought to direct the conduct of research involving human participants in a way that would recognise the social, economic, legal, regulatory and administrative arrangements that exist in developing nations. They have been widely adopted throughout the world. However, with the increasingly transnational nature of research, and the growing incidence of research involving large-scale clinical trials of medicines and vaccines, particularly following the emergence of HIV and AIDS, further revisions are under consideration.

5.15 In producing revisions, CIOMS/WHO also took into account the growing importance of epidemiological research for public health. In 1991 the **International Guidelines for Ethical Review of Epidemiological Studies** were published. These in turn informed the revised WHO/CIOMS guidance published in 1993 entitled **International Ethical Guidelines for Biomedical Research Involving Human Subjects**. Primacy was given to the protection of the rights and welfare of participants in research, and particularly those considered to be vulnerable. This guidance is currently being modified and the revised edition is expected to be published in 2002.

Other international guidance

5.16 Two further sources of guidance are routinely consulted with regard to the ethical conduct of research. Both draw on the Declaration of Helsinki. First, the **Guidance on Good Clinical Practice**[5] provides unified technical standards for clinical trials so that clinical data generated are mutually acceptable to regulatory authorities in the EU, the US and Japan. Secondly, the **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products**[6] from WHO lay down basic requirements for the ethical conduct of research. In addition, guidance entitled **Ethical Considerations in HIV Preventive Vaccine Research**[7] was published in 2000 by UNAIDS. Although designed for, and applied in the context of the development of vaccines, the guidance could be of relevance more generally.

National guidance for the conduct of research

5.17 The ethical principles outlined in Chapter 4 have been widely adopted at the national as well as the international level by those developed and developing countries which have established guidance to cover research involving human participants in their own territory. Guidance adopted

5 International Conference on Harmonisation (ICH) (1996) **Harmonised Tripartite Guideline. Guideline on Good Clinical Practice.**
6 World Health Organization (WHO) (1995) **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products.**
7 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document,** UNAIDS, Geneva.

in Denmark and Uganda is shown in Box 5.3. Some national guidance has the force of law, whilst other guidance is enforced by funding agencies for research as a condition of making a grant, or is simply voluntary codes of practice drawn up by national professional bodies, having persuasive force only. In most cases, the guidance applies within the country or its territories. In some cases, there are specific provisions relating to particular indigenous populations.[8] In New Zealand the importance of ensuring that research related to healthcare contributes to health development in Maori communities has been recognised.[9] Similarly, in Australia the National Health and Medical Research Council (NHMRC) has addressed the ethical issues that arise in connection with research related to health in Aboriginal and Torres Strait Islanders.[10] In other cases, there is specific recognition of the need to take differences in language and culture into account, for example, in the context of obtaining consent.[11]

BOX 5.3 Examples of national guidance: Denmark and Uganda

Denmark has published two laws on the ethics of research related to healthcare involving human participants.[1] These lay down the ethical principles to be considered by a national system of regionally-based committees carrying out review of the ethics of research with a majority of lay members. Since being established in 1980, all projects on healthcare in developing countries involving Danish scientists or Danish public funds have been evaluated under this system, and by the research ethics committees in the host country.

In 1997, **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda** were published.[2] These were the outcome of a process which began in 1994 to examine Ugandan guidance for the review of scientific research proposals involving human participants. The Guidelines set out general provisions for the protection of participants, along with requirements for institutional review committees, informed consent (including additional protections pertaining to vulnerable populations), and for monitoring and publishing research.

1 Act no. 503 of 1992 and Act no. 499 of 1997.
2 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda.

5.18 In a few cases guidance is explicitly applicable to research carried out under the auspices of national agencies in other geographical areas.[12] For example the US National Institutes of Health (NIH) **Guidelines for the Conduct of Research Involving Human Subjects at the NIH**[13] have been made explicitly applicable to research sponsored from within the US but carried out elsewhere.

8 For example, the National Health and Medical Research Council of Australia (NHMRC) (1999) **National Statement on Ethical Conduct in Research Involving Humans**.
9 The guidelines also emphasise the value of research partnerships between researchers and Maori communities on issues important to Maori health and the importance of encouraging them. To achieve these objectives, in 1998 the Maori Health Committee (MHC) of the Health Research Council of New Zealand published 'Guidelines for Researchers on Health Research involving Maori'. These were based on provisions laid down in the 19th century in the Treaty of Waitangi between the New Zealand government and Maori people. They place considerable emphasis on consultation with the Maori community to ensure that researchers did not offend cultural and tribal sensitivities in the course of research projects.
10 NHMRC published 'Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research' in 1991. These are directed at the Institutional Ethics Committees (IECs) in Aboriginal and Torres Straits Islander-controlled organisations which deal with ethical approval of project proposals from researchers in these organisations. As with the New Zealand guidelines, these emphasise the importance of consultation with the community-controlled health services and consent of the community for the research.
11 See the Brazilian 'Resolutions 196/1996, 251/1997 and 292/1999'.
12 See, for example, the US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**, and, in the case of the use of US Federal agency funds **Code of Federal Regulations Title 45 Public Welfare – Part 46 – Protection of Human Subjects** (1991).
13 US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**.

5.19 In the US, the ethical issues which arise when clinical research sponsored by the US is undertaken overseas were given detailed consideration in the US National Bioethics Advisory Commission's (NBAC) report entitled **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (2001)**. The Commission expressly discussed the problems that may arise when clinical research that is subject to US guidance is undertaken in developing countries. The report points out that this form of collaboration in research, although desirable, may cause controversy, particularly about the nature of the collaboration and the distribution of any resulting benefits. It also draws attention to the fact that 'Such controversies are perhaps more likely to occur when the nations involved do not share the same cultural, economic, political, and ethical perspectives, or when they are at different stages of development'.[14]

5.20 The NBAC Report emphasises the ethical and logistical problems that arise where research related to healthcare in developing countries is externally sponsored. The studies in question might simply be one way of helping the host country to address a problem in public health, or they might reflect an assessment by a research sponsor that the foreign location is a more convenient, efficient, or less problematic site for conducting a particular study or clinical trial. They might also represent a joint effort to address an important concern for healthcare faced by both parties'.[15] The NBAC Report draws attention to a more fundamental question regarding collaboration in research, particularly that which involves studies in the developing world: whether the existing rules drawn up by the US to regulate researchers working in the US are 'appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects'.[16]

The enforcement of guidance

5.21 As discussed earlier in the Chapter, most of the existing guidance on research related to healthcare does not have the force of law. However, the US Policy for the Protection of Human Subjects, which was inspired by the Belmont Report,[17] has legal force by being incorporated into the US Code of Federal Regulations. A few other countries, such as Denmark, have enshrined the main ethical principles governing medical research in law (see Box 5.3). Other guidance, such as the Council of Europe's **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine**[18] (Table 5.1) mentioned above, derive their authority through treaty obligations imposed on signatory nations.

---

14 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

15 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

16 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

17 The US National Research Act (1974) established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the Commission's charges was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to develop guidance to ensure research is conducted in accordance with these principles. The Belmont Report represented a summary of the basic ethical principles identified by the Commission in the course of its deliberations, see The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) **The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research**, Department of Health, Education, and Welfare, Washington, DC.

18 The Convention, which was adopted in 1997 to bring about the harmonisation of the standards in use within different European countries which have ratified the Convention, goes beyond the issues surrounding research on human participants and deals with a much wider range of medical practices, including issues that will arise out of genomics research and the clinical application of genetics and individuals' access to treatment. The Convention recognises, for instance, that standards are to be applied within local contexts and circumstances. A working party of the Council of Europe has recently prepared a detailed draft additional protocol on biomedical research that will be legally binding on all signatories within European States after its launch. In June 2002, the Steering Committee on Bioethics will review the Protocol. If agreed, it will then be submitted to the Parliamentary Assembly for consultation prior to submission for final adoption by the Committee of Ministers.

5.22 Most of the existing guidance, however, has merely persuasive force and is only enforceable through sanctions imposed on members of the profession or group which was responsible for the particular guidance. The Declaration of Helsinki, produced by the WMA, only binds physicians. Similarly, the CIOMS guidelines only bind members of the signatory organisations. Many involved in research related to healthcare today, however, are not members of the medical profession and thus may not be accountable under these guidelines.

5.23 In other cases, guidance can be enforced by the application of sanctions which will directly affect researchers who do not observe the operating standards and principles laid down. Guidance published by grant-giving agencies, for example, derives its authority from the fact that, unless it is adhered to, financial support for research will be withdrawn or not awarded. Pharmaceutical companies which contravene the guidance contained in the ICH's **Technical Requirements for Registration of Pharmaceuticals for Human Use** will find it difficult, if not impossible, to get a new medicine accepted by the regulatory authorities responsible for issuing licences to market products.

5.24 It is one thing to have guidance, it is another to interpret and apply it. Guidance is liable to different interpretations in different contexts. Furthermore, it is in the nature of such guidance that it does not seek to be comprehensive, given the increasing range of contexts that it is required to cover. For guidance to have the force of law, where it currently does not, a different approach would have to be adopted. The language would have to be clear and relevant to and applicable in a range of contexts and situations. To date this has not been achieved, as was highlighted in many of the responses to the consultation exercise carried out by the Working Party (Appendix 5). It may in fact be difficult to achieve given political and social pressures which come into play when, as a first step, attempts are made to harmonise and clarify the various elements of guidance. Meanwhile, whether or not guidance should have the force of law, there are obviously gaps in existing forms of guidance.

5.25 We have already emphasised that the external sponsors have a duty not to exploit the vulnerable when undertaking research related to healthcare in developing countries. The main aim of the guidance described in this chapter is to protect participants in research from harm, and particularly in the case of developing countries, from exploitation. In practice, researchers and sponsors are often confronted with guidance which is often generalised and even contradictory. Nor does the guidance generally take into account the special circumstances which characterise externally-sponsored research in developing countries. How best then can these countries protect their interests? We suggest two approaches that could be followed in which both developed and developing counties have a role. First, education and training can be arranged to develop expertise in developing countries for the purpose of active participation in the review of the ethics of externally-sponsored research. Secondly, the development of national guidance for the protection of participants in research offers developing countries the opportunity to set their own standards of protection in the light of international guidance. We consider each of these two approaches in turn.

Training

5.26 Guidance on the ethical conduct of research related to healthcare will be of little real value unless it can be understood and applied by sponsors of research, researchers and members of research ethics committees. Provision must be made for the education and training of those involved in research related to healthcare to ensure that guidance on ethical conduct is clearly understood and implemented. We strongly urge that such education and training should be made available not only to researchers and others in developing countries, but also to researchers in developed

countries so that a common understanding is established. **We conclude that in any revised or new guidance the provision of training in the ethical conduct of research should be a requirement placed on all involved in the sponsorship of research in developing countries.**

5.27 Research related to healthcare is not conducted exclusively by medically qualified practitioners. On the contrary, much research in this area is now necessarily multi-disciplinary. Researchers may be biochemists, molecular and cellular biologists, geneticists, psychologists, sociologists, anthropologists or others. All of these should be brought within the ambit of the guidance on ethics that address responsibilities to research participants. **We recommend that national and international sponsors of research ensure that provision is made for education and training in the ethics of research of all of those professionals involved in research related to healthcare to ensure that the requirements of relevant guidance on ethics are met.**

The development of national guidance

5.28 As we noted above, researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometime conflicting guidance. A number of developing countries (and many developed countries) have responded to this difficulty by developing their own national guidance to provide a framework for the review of the ethics of research related to healthcare in their countries. Such guidance, which should be based on an interpretation of the international guidance set out in this chapter, generally applies to both externally-sponsored research and internally-funded research. Developing countries which have taken this step include South Africa, Uganda, Nepal, Thailand, India, and Brazil (Appendix 1, Table 1). The development of expertise to formulate national guidance may also require education and training. **We encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application**. We take the view that, taken together, the development of national guidance and the strengthening of the process of review of the ethics of research related to healthcare will afford a further layer of protection to participants in externally-sponsored research studies and should be priorities for developing countries and sponsors of research.

Section 3

The issues

Chapter 6

Consent

Introduction

6.1 Respect for persons is a fundamental moral duty. In research relating to healthcare, this duty requires that we do not act against a person's wishes. His or her consent to participate in research must thus be obtained. The duty upon those conducting research ordinarily to obtain consent is widely recognised in national and international guidance and in legislation (see Box 6.1).[1] The three elements of consent reflected in ethics, national legislation and human rights law are that it must be informed, given voluntarily, and given by a person competent[2] to do so. In this chapter we will focus on two elements of consent which are particularly relevant to externally-sponsored research conducted in developing countries: the provision of information to participants in research; and the requirement that consent to research be given voluntarily. Appropriate means of documenting consent to take part in research will then be considered.

6.2 When externally-sponsored research is conducted in developing countries, a range of issues arise in seeking consent to take part in research. With regard to informing potential participants, concepts that are common in research, such as the idea of randomisation, or of using placebos, may be unfamiliar to the culture in which the research is being conducted. As regards the voluntariness of consent, in some communities it is common for a spouse or senior member of a family to assent to healthcare (and by extension, to research) on behalf of a woman or adult children (see paragraph 3.18). In addition, access to better healthcare and other benefits which may accrue from taking part in research may act as powerful inducements, casting doubt on the true voluntariness of a participant's consent.

6.3 In research, in addition to their responsibilities to individual participants, researchers are seeking to conduct scientifically sound research that will provide generalised information that can improve healthcare. When medical care is combined with research, researchers may make different choices about clinical measures than they would if the participants' best interests were their only concern. For example, during research, healthcare workers may administer placebos or take blood samples for tests that will not benefit participants directly, in order to obtain information. The potential conflict between the dual roles of healthcare providers in such circumstances means that the process for obtaining consent to research must be rigorous and that participants must be made aware of the dual purpose of research before being asked to consent to it. Conversely, when research does not contain any therapeutic component, this fact must also be made clear to prospective participants.

Information

6.4 A prospective participant in research must be provided with information about the proposed research before any consent to participate can be considered to be valid. The ethically significant requirement is that consent to research be *genuine*.[3] Ensuring that consent is genuine

1 US Regulations make provision for waiver of consent under four conditions: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116d). The UK Medical Research Council 1998 guidance entitled 'Guidelines for Good Clinical Practice in Clinical Trials' paragraph 2.9 states that 'freely given informed consent should be obtained from every participant prior to clinical trial participation' though this does acknowledge that situations may exist where this is not possible (e.g. emergency settings) and in such cases, procedures agreed in existing guidelines should be followed provided favourable opinion has been given by the appropriate independent ethics committee. The UNESCO's Universal Declaration states that 'limitations to the principle of consent and confidentiality may only be prescribed by law, for compelling reasons within the bounds of public international law and the international law of human rights' (Article 9).

2 A person is considered to be competent if they are able to understand information about the proposed research.

3 Nuffield Council on Bioethics (1995) **Human Tissue: ethical and legal issues**: Paragraph 6.20, Nuffield Council on Bioethics, London.

BOX 6.1 Examples of guidance on consent

The Helsinki Declaration (2000 revision) requires that each potential subject must be adequately informed about:

- the aims of the study and methods to be used;
- the sources of funding and possible conflicts of interest;
- the institutional affiliations of the researcher;
- the anticipated benefits and potential risks and the follow-up of the study;
- the discomfort it may entail; and
- the right to abstain from taking part in the study, or to withdraw from it at any time, without any reprisals.[1]

The CIOMS/WHO 1993 Guidelines set out, in some detail, the 'essential information' that must be provided to research participants.[2] These go further than the Declaration of Helsinki and include:

- the alternative procedures or treatments available;
- what responsibility, if any, lies with the investigator to provide medical service to the subject;
- provision of free treatment for injuries related to research.

A detailed list of the duties of investigators in obtaining consent which is properly informed is provided, including:

- encouraging the participant to ask questions;
- avoiding possible deception; and
- obtaining new consent if the conditions or procedures involved in the study change.[3]

1 World Medical Association (WMA) (2000) **Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects**, adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000: paragraph 22.

2 See CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**: Guideline 2. This should be regarded as a minimum and the guidance in the commentaries on several of the other guidelines outlines circumstances where additional types of information should be conveyed.

3 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**: Guideline 3.

requires care in detecting a lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate mis-description of what is proposed, lack of disclosure of material facts, or conflicts of interest.

6.5 To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made. It must include such matters as the nature and purpose of the research, the procedures involved, and the potential risks and benefits. National and international guidance sets out the factors which prospective participants must be informed of (see Box 6.1).

6.6 Requirements of particular relevance to externally-sponsored research conducted in developing countries include the need to ensure that participants be provided with information about the study in a language that they can understand, and at their level of comprehension.[4] The importance of allowing potential participants the time to ask questions, obtain answers and to reflect and give due consideration to their participation is also emphasised.[5]

6.7 An awareness of the social and cultural context in which the research is to be conducted is required, so that communities and individuals can be informed of any

4 For example, the commentary accompanying Guideline 2 of the CIOMS in collaboration with WHO (1993) guidance explicitly states that 'Informing the subject must not be simply a ritual recitation of the contents of a form. Rather, the investigator must convey the information in words that suit the individual's level of understanding'.

5 See, for example, National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda:** p. 32; Indian Council of Medical Research (2000) **Ethical Guidelines for Biomedical Research on Human Subjects**: General ethical issues, 2i.

aspects of the research that may cause them particular concern. These may include such matters as the amount of blood to be taken, or whether participants will be physically examined by researchers of the opposite sex. The process of informing participants about research must also provide opportunities for individual participants to ask about such matters as whether the research may affect their ability to carry out their livelihood. Consent may sometimes need to be sought in the presence of another person, or group, so that the individual feels supported, and more able to ask questions or voice concerns. In other circumstances, privacy may be essential; for example if the prospective participant wants to discuss confidential issues, such as HIV status, with the researcher.

6.8 Healthcare professionals should respect the limits of individuals' understanding and capacity to deal with difficult information and allow time for them to reflect and ask questions. For example, participants may have little understanding of the biological processes that take place in their bodies, or have different beliefs about the causes of disease, which make it more difficult to comprehend the information given. If all reasonable care is exercised, genuine consent may be given.

Issues which may arise when informing participants about research

6.9 In some developing countries, during routine clinical care, information about a diagnosis of a serious disease such as cancer may be provided to a patient's family, rather than to the patient.[6] In such circumstances, the requirement that genuine consent be given to participation in research into appropriate cancer treatments will conflict with standard medical practice, which is to withhold the diagnosis of cancer from a patient.

6.10 In some cultures it is customary for a physician to advise a patient which treatment to take, rather than discuss various treatment options. In Vietnam, for example, it has been suggested that: 'it is unacceptable for a physician to openly express uncertainty with regard to what is the best treatment.'[7] In such circumstances, it has been argued that it is not appropriate to comply with the requirement that participants be informed about the options for treatment which are available, and that there is uncertainty about which will prove to be the best.[8]

6.11 In Chapters 3 and 4 we discussed the need to be sensitive to the cultural context in which research is conducted. However, this does not mean that cultural practices must be accepted uncritically. In the circumstances outlined above, there is a tension between the requirement that genuine consent to research be obtained from participants and cultural contexts in which giving certain information is not customary. The Working Party has considered these competing interests and has concluded that obtaining genuine consent to research from participants is vital in ensuring that respect for persons is promoted. Without appropriate information, participants in research may be harmed by being exposed to risks or dangers that they would prefer to avoid. In addition, they will be denied the opportunity to learn more about their condition, possible treatments, and any beneficial outcomes of the research. Consequently, when research is conducted in contexts in which the information about diagnoses and options for treatment is not normally provided, care and sensitivity will be required to design appropriate consent procedures, so that participants receive appropriate information about research and genuine consent may be given.

---

6 See, for example, Moazam F (2000) Families, patients, and physicians in medical decisionmaking: a Pakistani perspective, **Hastings Center Report**, November–December: 28–37 and Macklin R: The doctor–patient relationship in different cultures, in Macklin R (1999) **Against Relativism. Cultural Diversity and the Search for Ethical Universals in Medicine**, OUP, New York.

7 Love RR and Fost NC (1997) Ethical and regulatory challenges in a randomized control trial of adjuvant treatment for breast cancer in Vietnam, **Journal of Investigative Medicine**, 45(8) 423–31.

8 Love RR and Fost NC (1997) Ethical and regulatory challenges in a randomised control trial of adjuvant treatment for breast cancer in Vietnam, **Journal of Investigative Medicine**, 45(8) 423–31.

Understanding information

6.12 A number of methods have been used by researchers in developing countries to ensure that information about research has been provided to participants in an appropriate manner. These include:

- providing information to participants at meetings, so that they have an opportunity to discuss the proposed research with others and pose questions for clarification
- providing information through health workers (and particularly female health workers when the research will involve women), rather than physicians so that participants feel more able to discuss and ask questions
- providing information about a research project in various ways that are appropriate to the community (i.e. in parts of Africa, information has been supplied on audio or video tape, on the radio and through ballad singers)
- providing information over a period of time, so that prospective participants have time to consider it and raise questions.

We concluded in Chapter 3, that consultation with the community in which research is to be conducted will be required to determine which methods of providing information will be most appropriate for a given research project. In some communities, particular care will need to be taken to ensure that the methods of providing information and aiding understanding which are adopted will ensure that the information will reach all members of the community. For example, if public meetings are used, it must be borne in mind that young women may feel unable to ask questions during such a meeting.

6.13 Information about research should be provided in a form that is likely to be comprehensible to a prospective participant. In some circumstances, healthcare workers, some of whom may have been recently recruited, will be responsible for explaining the research to prospective participants. Clearly, researchers will need to provide appropriate training to ensure that healthcare workers understand the research and can pass on accurate and comprehensible information.

6.14 A number of methods have been used by researchers to assess whether participants in research have understood information provided about the proposed research. For example, prospective participants may be asked to pass a test before consenting to participate in the research. Such tests are designed to ensure that the relevant information about the research has been understood. Alternatively, following the provision of information, prospective participants may be asked to explain what they have understood about the research.

Complex and novel concepts

6.15 Some concepts used in research may be difficult to explain in a understandable manner, particularly in populations with entirely different beliefs about the causes of illness and little familiarity with biomedicine. In such circumstances, researchers will need to consult communities to determine how concepts can be explained in a comprehensible manner. One example is to incorporate local belief systems into the process of providing information. For example, the researchers might say: 'Although I as a doctor believe that the disease is caused by germs (i.e. a virus or bacterium), I understand that you believe that it is caused by a demon. I respect the fact that you have this belief and I should like you to try this medicine to remove the disease. Removing the disease is more important to us both than whether we think it is caused by germs or a demon.' Some biomedical researchers resist this approach on the ground that biomedical interventions should not perpetuate what they regard as 'unscientific' or 'superstitious' beliefs and

practices. However, in some circumstances it will be possible to strike a balance between such a stance and the harnessing of local beliefs in the interests of improving participants' understanding of research.

6.16 Participants in research in developing (and developed) countries may find concepts such as randomisation, genetic research and placebos incomprehensible.[9] Indeed, many languages will not have terms for such concepts. Researchers in developing countries have demonstrated that such concepts can be successfully explained, but again, care will be required to do so (see Box 6.2).[10]

BOX 6.2 Good practice in explaining research concepts[1]

To illustrate the principle of randomisation and the possibility that one of the vaccines might fail, in one research project a familiar agricultural example was used: the evaluation of fertilizers or of seed varieties on randomised plots, a procedure familiar to farmers in the area.

Another study required the concept of immunology and the role of immune cells to be explained. Immune cells were likened to people who guard houses, as a type of watchman, with blood depicted as containing particular kinds of watchman.

1 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research; Clinical Trials in Developing Countries. Volume I**, National Bioethics Advisory Commission, Bethesda.

6.17 In many developed countries, in response to the interests of relatively sophisticated populations and following concerns about legal liability, detailed and complex information is provided to prospective participants, setting out possible risks accompanying research. In both developed and developing countries such information may be poorly understood and, to the degree it may be understood, unduly alarming, particularly in populations with little experience of discussing possible side-effects or risks accompanying treatment.[11] For example, during the Working Party's fact-finding meeting in India, one physician noted that in rural areas the trust in doctors was so great that if a doctor described six possible side-effects of a treatment then participants often expected to experience them all.[12] Consequently, collaboration will be required with local researchers and representatives to ensure that information about risks and the likelihood of their occurrence is provided to participants in a comprehensible manner.

Voluntariness

6.18 As discussed above, for consent to be genuine, it must be freely given. In some societies in developing countries, it is considered inappropriate for an individual to be asked to consent to participate in research without the community, or leader(s) of the community, having been consulted first (see Chapter 3). In other groups, a family or leader(s) of the community may be

9 In one study in the UK an exploration of participants' understanding of randomisation showed that: (1) Most trial participants were able to recall and describe various aspects of randomisation, including the involvement of chance, comparison and concealed allocation, (2) The majority found the concept of randomisation difficult to accept and developed other accounts to make sense of their experiences, (3) The use of terms which have different meanings to lay and professional (such as trial and random) can cause confusion among participants, (4) Providing clear and accurate patient information is crucial, but to give truly informed consent, patients may need time to discuss the purpose of clinical trials and concepts such as randomisation. See Featherstone K and Donovan JL (1998) Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial, **BMJ**, 317 1177–80.

10 See National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Maryland, USA : 40–41, for description of innovative ways of presenting information to research participants.

11 See Marshall PA (2001) The relevance of culture for informed consent in US-funded international health research, in National Bioethics Advisory Commission (NBAC) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**. See **Volume II Commissioned Papers and Staff Analysis** for a discussion of issues around disclosure of risk in informed consent.

12 Personal communication, Working Party fact-finding meeting.

BOX 6.3 The role of the community when consent is sought

Some national codes specifically address the role of the community and its leaders in the process of informing participants about research and obtaining consent. For example, the guidance in Brazil recognises the need to be sensitive to cultures and communities and requires that in the case of communities with a separate culture, including indigenous populations, prior consent must be obtained from leaders of the community before consent from prospective participants is sought. The importance of making efforts to obtain the consent of each participant in a study is also emphasised.[1]

Guidance on research in New Zealand recognises in research with Maori communities the tribe and extended family groups have some authority over their members' participation in research. The guidance, therefore, emphasises the need at all stages of a research project for consultation with the Maori communities who will participate in it.[2] However, this does not remove the need to obtain the consent of each participant in research.

Australian guidance requires that with research involving aboriginal and Torres Strait Islander communities there must be written evidence of the assent of the community, or justification why it has not been possible to obtain it.[3] There must also be evidence of the process for obtaining the consent of each participant.

1 See, for example, Paragraph IV (3e) of the Brazilian Resolution No. 196/96 on Research Involving Human Subjects which states that 'in communities with a different culture, including Indigenous communities, prior consent must be obtained from the community, through its leaders, without foregoing, however, efforts to obtain individual consent.'

2 The Maori Health Committee of the Health Research Council of New Zealand (1998) **Guidelines for Researchers on Health Research involving Maori.**

3 National Health and Medical Research Council of Australia (1999) **Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research.**

expected to make decisions about participating in research on behalf of women and older children, who would make their own decisions in other societies. An additional factor which may affect the voluntary nature of consent to research is any inducements accompanying invitations to participate in research. These are considered in turn.

The assent/involvement of the community

6.19 In some societies it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders. Three such situations can be distinguished:

- consultation is required with the community before individuals are approached about research
- permission from a leader(s) of the community is required before any research is discussed with the community or individuals
- the leader of the community is considered to have the authority to enrol participants in research.

6.20 In each of these circumstances, to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm relationships within that community and between a community and researchers. The role of the community in the process of obtaining consent is specifically recognised in some countries' guidance on research (see Box 6.3).

6.21 The third of the situations set out in paragraph 6.19, where the leader(s) of the community or a senior family member customarily has the authority to make decisions on behalf of others, including whether they will participate in research, is the most problematic. In some developed countries, in limited circumstances and with strict safeguards, the law permits a proxy to consent to research on behalf of children and adults who do not have the capacity[13] to make such

13 We use the term capacity to mean a participant who is competent to consent to research themselves, i.e. if they are able to understand information about the proposed research.

decisions themselves. However, as discussed in paragraph 3.18, the notion of consent on behalf of others is more widespread and ingrained within some cultures in developing countries.

6.22 We noted in Chapter 4 that we cannot avoid the responsibility of taking a view when the two aspects of respect – respect for culture and respect for persons – come into conflict with one another. We are of the view that the fundamental principle of respect for persons requires that participants who have the capacity to consent to research should never be subjected to research without such consent. Some prospective participants may choose to delegate to another, the decision about whether or not to participate in research. Where such delegation has not taken place, to allow others to make decisions on behalf of participants in research who have the capacity to consent themselves would be to deny that all people are moral equals and deserve to be treated in ways that promote their dignity and wellbeing. We conclude that assent from others may be necessary before research is conducted, but that it is not sufficient: individual participants must receive appropriate information about the research and should be asked to give consent. To ensure that individual participants can make up their own minds without undue communal pressure, anonymity for those who wish to decline to participate in research should be assured. **We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected. Researchers must not enrol such individuals and have a duty to facilitate their non-participation**. A summary of the reasoning behind this conclusion is given in Box 6.4.

BOX 6.4 Summary of arguments about genuine consent

The principle of respect for persons requires that we do not conduct research without their consent.

BUT

Sensitivity to other cultures requires that researchers pay attention to the context in which research is conducted, including customs and traditions.

NONETHELESS

Sensitivity to other cultures cannot override the central requirement of respect for persons, which requires that we refrain from conducting research without consent. This is a fundamental principle, which it is important to promote so as to empower vulnerable populations.

THEREFORE

Genuine consent to research must be sought from all participants in research.

AND

There is also a duty to develop or implement innovative practices with regard to providing information and to ensure that consent to research is freely given.

Refusing to participate in research

6.23 One respondent to our public consultation from South Africa, asked, 'How can women – who are known, can be identified and found, and are dependent on the available health facilities which simultaneously function as research sites – be made to feel that their participation is voluntary?'[14] The real significance of this question lies in the extent to which such women could feel free to say no to research. If consent to research is to be genuine, participants will need to be made

14 Response by the HIV/AIDS Vaccine Ethics Group (HAVEG) at the University of Natal, South Africa, to the Working Party's Consultation.

aware that they may choose to refuse to take part, or withdraw at any time and that this will not affect their future healthcare.[15] Consultation with local communities and researchers will be necessary to design an appropriate consent process that takes account of these matters. When concerns arise about whether or not participants feel able to decline to participate, it may be appropriate to have some form of external audit of the process for obtaining consent and its outcomes.

6.24 The Helsinki Declaration cautions that, where a subject is 'in a dependent relationship with the physician or may consent under duress', consent should be obtained by an independent physician. However, where participants have great respect for physicians and little awareness that they can refuse to participate in research, it may be immaterial whether it is a physician whom they know or an independent physician who asks for their consent. Researchers must take account of this respect for physicians and develop means to ensure that participants know that they can refuse to participate in research. In some circumstances it may be easier for participants to refuse to participate if they are speaking to a healthcare worker or interpreter, rather than a physician. Care must be taken, therefore, to ensure that research workers and interpreters realise that their role is to provide accurate information in an understandable manner to prospective participants, rather than to enrol as many participants as possible.

Inducements

6.25 Participants in research in developing and developed countries have a range of motivations for taking part in research (see paragraph 3.21). One motivation that may be offered to prospective participants is a benefit, such as a financial payment, or healthcare in the future, or for a period of time, for themselves or their families. Inducements which research ethics committees in developing countries have considered acceptable include money in the form of payments for travel, inconvenience or work lost, food, photographs or film, and healthcare for individuals and their families during research.[16]

6.26 The point at which inducements become inappropriate is not always clear. Principle 11 of the 1991 CIOMS guidelines draws attention to the fact that 'it can be hard to draw the line between exerting pressure, or offering inappropriate inducements, and creating legitimate motivation'. However, it is possible to offer some guidance to assist attempts to draw this line. It should be remembered that without some prospect of benefit, either for themselves or others, most individuals would be unlikely to consent to participate in any research. We consider that researchers should, at the very least, aim to ensure that participants are not placed in a worse position by participating in research. The payment of reasonable expenses incurred by the participant, or remuneration for loss of earnings suffered is generally considered to be acceptable and may be necessary in developing countries where high unemployment means that participants are only able to take part in research programmes with such support.[17]

6.27 An inducement may persuade an individual to change his or her mind about entering a research project, but this in itself is not enough to make it inappropriate. For example, it may well be a rational choice not to take part in a research project, which may or may not provide any personal

15 A number of national laws and declarations, including the Helsinki Declaration make clear that potential participants in a research project should be told beforehand that they have the right to abstain from participation, or, if they do take part, to withdraw from the study at any time without reprisal. This principle was also included in the CIOMS/WHO 1993 guidance which emphasises the right of the subject to refuse to participate in the study, or withdraw from it without penalty or loss of benefit. Similar provisions have been imported into a number of the national ethical codes or laws.

16 Nuffield Council on Bioethics (1999) **The Ethics of Clinical Research in Developing Countries**, Nuffield Council on Bioethics, London: paragraph 44.

17 Principle 12 of the 1991 CIOMS guidelines states that it is acceptable to repay expenses incurred, and that promises of compensation and care in case of damage, injury or loss of income are not to be considered as inducements.

benefit, unless some extra benefit is provided. However, inducements can also change a prospective participant's mind in a less benign manner, so that their calculation of the costs and benefits of the research results in their decision that the benefit offered by the inducement outweighs all risks, however substantial. This could cause individuals to expose themselves to risks or potential harms that they would ordinarily view as unacceptable, and it is in such circumstances that the inducement would be inappropriate.[18]

6.28 The greater the inducement, the more likely it is to be inappropriate, because it may cause an individual to ignore or devalue his or her concerns about the risks involved in a research project. Special care must be taken, therefore, when research is accompanied by significant risks. The more serious the risks faced by a participant in research, the more closely the level of inducement should be scrutinised, to ensure that it is not inappropriate.

6.29 It is an inescapable fact that people who are ill may place great weight on a possible health benefit, even if the probability that it will occur is relatively low. This means that involvement in research which, of necessity, involves medical treatment, may amount to an inducement since the participant will receive medical treatment for his or her condition and may thus be less likely to refuse. This does not necessarily mean that the individual has been exploited. However, when participants are ill and do not have alternative ways of receiving treatment, the possibility for exploitation is greater. The CIOMS guidelines note that 'someone without access to medical care may be unduly influenced to participate in research simply to receive such care'.[19]

6.30 Guaranteed healthcare or a payment offered to individuals on condition that they take part in a research project could be considered to be exploitative if otherwise there is a very low probability of receiving such a benefit. This contrast in benefits, depending on whether an individual enrols in research is particularly important in developing countries (see Box 6.5). Research ethics committees should bear this in mind when assessing whether it is acceptable to conduct a research projects which may involve more than minimal risk. In such circumstances special care should be taken when determining the nature of additional healthcare to be offered to participants as an inducement.

BOX 6.5 Views on the benefits of taking part in research

'How useful is the issue of informed consent in the Philippines and other developing countries, since it is always the poor in trials who cannot afford the drugs on the market? It is their only realistic form of treatment and they are not truly free to decide not to participate.'[1]

'When the project first ended, the staff told me about a new project I might join and I decided to enrol again. If there were no studies, I would not have the opportunity to take anti-HIV medication.'[2]

'The study staff gives good advice and when this project is over I hope I can enrol in another study. For that matter, I hope there will be new studies for me to participate in all the time. If there would be no more studies, I don't know if I would have the strength to go on, as I would not know where to get drugs outside of clinical trials.'[3]

1 See Kenyon G (2000) Informed consent means little when drug trials are only means of treatment, **Medscape.com**, 26 September.

2 HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration) (2000) **HIV-NAT. The HIV Netherlands Australia Thailand Research Collaboration. A model for HIV-AIDS clinical research in a developing country**, UNAIDS, Geneva: 42.

3 HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration (2000) **HIV-NAT. The HIV Netherlands Australia Thailand Research Collaboration. A model for HIV-AIDS clinical research in a developing country**, UNAIDS, Geneva: 41.

18 The CIOMS 1993 guidance states that payments should not be so large or provision of medical services so extensive 'as to induce prospective subjects to consent to participate ... against their better judgement'.

19 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**: Commentary on Guideline 4.

6.31 We suggest when assessing the acceptability of inducements to participate in research in developing countries, those designing the research and research ethics committees should pay particular attention to:

- *harmfulness:* whether there are potential risks to the participants' health from taking part in the research
- *proportionality:* whether the inducement being offered is in proportion to the risks and costs to the participant involved in the research
- *vulnerability:* whether guaranteeing substantial benefits for taking part in research is more likely to constitute an undue inducement because prospective participants are especially vulnerable, for example because they have a terminal or chronic illness.

6.32 The CIOMS guidelines note that the propriety of inducements must be 'assessed in the light of the traditions of the culture'.[20] For example, some cultures may have a tradition of gifts or exchanges which will make some forms of inducement more appropriate than others. The majority of respondents to our public consultation noted that many decisions about which inducements are appropriate will depend on local circumstances. In such cases, local knowledge will be essential in making appropriate distinctions. One respondent commented:

> The level [of compensation] would have to be determined locally e.g. what is considered an appropriate sum to cover time and inconvenience in the US (say $50) would be equivalent to several years earning in rural Uganda.[21]

We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.

Recording consent

6.33 As regards consent to research, many of the concerns raised by respondents to our public consultation and by those who attended our fact-finding meetings related to the process by which consent was recorded. A common observation was that consent forms often seemed to be designed to protect sponsors of research, pharmaceutical companies and researchers, rather than to provide prospective participants with appropriate information. The most common criticisms were that information and consent forms were too long and contained language that was inappropriate at best, or confusing and misleading at worst (see Box 6.6).

6.34 As we have made clear, it is the substance of the process for obtaining consent which is important, rather than the procedures used to record or document the process. Wherever research is being conducted, an appropriate and transparent procedure for obtaining genuine consent is required. A written consent form is merely evidence of what was agreed. If a prospective participant in research is given a consent form to sign, without there being an appropriate process for receiving information and then giving consent, a genuine consent to participate in research will not have been given, irrespective of whether or not a form has been signed.

20 CIOMS (1991) **International Guidelines for Ethical Review of Epidemiological Studies**, CIOMS, Geneva: Principle 11.
21 Response by Dr Dilys Morgan to the Working Party's consultation.

6.35 The purpose of a consent form is to record what has been agreed between the researcher and participant. Consequently, a consent form will not protect participants in research from possible harm, except to the extent that it discloses information which may lead to a prospective participant choosing whether to take part in the research and run a certain risk. Likewise, a consent form is neither an appropriate nor effective medium for seeking to limit legal liability for any possible harmful consequences of research.[22] Questions about liability for harm arising from participation in research should be agreed by the parties involved in designing, sponsoring and conducting the research before the research begins (these questions will be governed by law in some jurisdictions). Participants in research in developing countries will need to be made aware of who will be responsible for looking after them should they suffer any harm as a result of research participation, and, unless informed, may be less likely than participants in developed countries to realise that they have avenues of redress.

BOX 6.6 Consent forms: criticisms from researchers

'The mechanisms of obtaining informed consent in developed countries evolved in communities that are literate and generally aware of modern health practices. Researchers can therefore engage the potential subjects on the basis of pre-existing scientific knowledge and concepts. To use the forms that were designed in such circumstances to obtain informed consent in a non-literate community that operates on different concepts of health and disease, would be an exercise in self deception.'[1]

'Insistence by regulatory authorities on the use of complex consent forms devised for use in litigious Western societies is inappropriate.'[2]

'Consent forms can be too long. Patients don't understand them. It is quality not quantity that is important ...'[3]

'When most of a population was illiterate, participants were very cautious, they [didn't] know what they were signing or whether it could be used against them. Many researchers therefore considered verbal consent to be very important but did not require written consent.'[4]

1 Response by Professor Adetokunbo Lucas to the Working Party's consultation.
2 Response by Professor Brian Greenwood to the Working Party's consultation.
3 Comment made during Working Party's Fact-finding meeting, Chennai, India, 21 January 2001.
4 Comment made during Working Party's Fact-finding meeting, Madison Hotel, Washington, USA, 23 March 2001.

6.36 In paragraphs 6.4–6.7 we discussed the information which participants need to be given before their consent to research should be sought. Various forms of guidance give detailed indications of the matters about which participants should be informed.[23] It should always be remembered that such devices as information sheets and consent forms are intended to assist the consent process. Researchers will need to refer to the relevant guidance and consider which matters are relevant to their research and to the context in which the research is to be conducted, and how to express the information they seek to convey. Forms which are long, complex and inappropriate for the cultural context in which they are being used, are likely to confuse, rather than inform, participants in research, and should not be approved by ethics research committees. Some ethics research committees, such as, for example, the committee in The Gambia prefer that all consent forms be no more than one page in length, and

22 In many jurisdictions there are legal restrictions on the ability of individuals (such as researchers) and institutions (such as sponsors of research) to limit liability for injury caused by their own fault. Thus, even if a clause attempting to limit liability is included in a consent form, it may have no effect. However, participants in research who have signed such a form may believe that they have waived their rights and be less likely to pursue treatment or compensation for harm caused by research.

23 For example, Guideline 2 of the CIOMS 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects specifies 10 pieces of essential information which should be given to prospective research participants, including: the aims and methods of the research, the benefits that might reasonably be expected to result to the research participant or to others as an outcome of the research, any foreseeable risks or discomforts, the extent of the investigator's responsibility, if any, to provide medical services to the research participant, confidentiality of participant data and arrangements for compensation for research-related injuries.

that appropriate language be used. Information sheets, which can be taken home and read, shared, translated and re-read, may be longer but still need to be written clearly.

Situations where consent forms are inappropriate

6.37 There are circumstances in which, while genuine consent to research can be obtained, it may be inappropriate to ask participants in research to sign consent forms, no matter how well designed. One obvious example is when research is being conducted in an illiterate population. The Working Party considers that it is not consistent with the duty of respect for persons to require a prospective participants to 'sign' a written consent form that they are unable to read.[24] Some forms of guidance explicitly recognise that written guidance will not be appropriate in all circumstances and set out appropriate safeguards.[25] In its recent report, the US National Bioethics Advisory Commission recommended:

> US research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms. Ethics review committees should grant such waivers only if the research protocol specifies how the researchers and others could verify that research participants have given their voluntary informed consent.[26]

6.38 In other societies, literate participants may fear that signing forms may link them to particular organisations and leave them open to retribution from repressive regimes.[27] In some cultures, participants' only experience of signing forms may be in relation to tax documents or court proceedings. Thus, signing a consent form is likely to have negative connotations, making otherwise willing participants less likely to take part. In one research trial examining the consequences of domestic violence, it was considered inappropriate to ask female participants to sign a consent form before enrolling them in the research because of their concerns that signing a form would mean that a record of victims of domestic violence would be kept and this might lead to them suffering more harm.

6.39 If requesting that participants sign consent forms is inappropriate (see Box 1.1), other means of recording their genuine consent to participation in research is required to protect them from being enrolled in research that they have not consented to. In many circumstances, the research worker who is informing the participant will sign a form stating that the appropriate information was given and verbal consent received. An alternative is to record consent on audio tape. As an additional safeguard, it is desirable for an independent witness to observe the verbal consent. In some circumstances it may be more appropriate to have an independent witness to observe the process of providing information to the community and individuals, rather than observing the verbal consent to participate in research (see Box 6.7).

24 However, in such populations participants may find it useful to take written information sheets away with them for discussion with literate family members or colleagues, and for future reference.

25 For example, the Declaration of Helsinki (2000) (paragraph 22) states that where written consent cannot be obtained, verbal consent must be fully documented and witnessed. **The Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa** (2000) in referring to vulnerable communities state that where a person is illiterate 'verbal consent ... should be obtained in the presence of and countersigned by a literate witness' (paragraph 3.5).

26 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Recommendation 3.11.

27 The 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda' note that a research participant's wish not to execute a written informed consent form should be honoured but the investigator must obtain oral informed consent and document such. NBAC (2001) recognises that this rejection stems from Uganda's past experience of torture and persecution of individuals found to be associated with particular enterprises and that individuals may consequently be reluctant to sign a form which associates them with certain activities.

6.40 **Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given. Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent.**

BOX 6.7 Witnessing verbal consent

Some forms of large-scale research in developing countries, such as research into vaccines, may involve many thousands of participants. In such circumstances information may be provided in a number of ways, including by television, radio and articles in newspapers. In addition, regional, local and community meetings may be held to discuss the research. If participants wish to take part in research, they will then attend one of a number of sites where the vaccine is to be administered. In such circumstances, where there is a limit to the resources and appropriately trained staff available, it may be more appropriate for the provision of information to be witnessed, rather than to attempt to provide witnesses at the field sites to confirm that each individual who attends wishes to participate in the research.

Chapter 7

Standards of care

Introduction

7.1 This chapter examines the ethical considerations that arise when researchers determine the standards of care to be provided for participants in research. In particular, we focus on whether participants in the control group of a research trial should be provided with a universal standard of care, regardless of where the research is conducted (see Box 7.1). This issue was highlighted in 1997 in the dispute about the standard of care to be provided to those involved in clinical trials investigating the prevention of the transmission of HIV from mother to child (see Box 1.2).

BOX 7.1 Standards of care

We are aware that use of the term 'standard of care' has been criticised in the context of research related to healthcare because of its ambiguity.[1] Rather than introduce a new term, we have chosen to adopt the term 'standard of care' in the Report, and define it as: 'the nature of the care and treatment that will be provided to participants in research'.[2] We use the term simply as a generic description of the range of preventive or curative treatments (or lack of them) and diagnostic interventions which are made available to participants.

We use the term 'universal standard of care' to indicate the best current method of treatment available anywhere in the world for a particular disease or condition. For most diseases and conditions such a standard of care is routinely available to only a small proportion of the world's population.

1 See for example, National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: 9 and Benatar SR and Singer PA (2000) A new look at international research ethics, **British Medical Journal**, 321 824–6.

2 While the term 'standard of care' is used in law to refer to the standard of treatment that a court would conclude that a reasonable physician would provide in the circumstances, the term is used here to describe what happens in practice, whether or not it could be considered to be reasonable or appropriate.

7.2 Research conducted in developing countries should be relevant to the healthcare needs of that country (see Chapter 2). However, debate has arisen about how the requirement that research be relevant should be balanced against the need to avoid exploitation of participants in research in developing countries. The debate arises in the following way. Some argue that when research is externally sponsored, participants in developing countries should receive the same standard of care and treatment as would participants in the country sponsoring the research. In contrast, others claim that the requirement that participants be offered the same standard of care and treatment, whether or not they live in developed or developing countries, would prevent some forms of research from being carried out which could lead to improved healthcare in developing countries. For example, researchers may seek to determine whether a new treatment for a disease is better than the one currently available in a developing country. To do this they may want to compare the new treatment with the current treatment that is available within that country, rather than with another, but much more expensive treatment that is available in developed countries.

Existing guidance

7.3 The existing international and national guidance embraces a range of interpretations about what standard of care should be provided during the conduct of research (see Table 7.1 and Appendix 1 Table 2). The Declaration of Helsinki (2000) is the primary source of guidance on which the majority of other guidance draws. It is, therefore, our starting point. The relevant provisions are set out in Table 7.1. In the context of developing countries, the best current method of treatment (paragraph 29) is frequently not accessible and the majority of people are 'economically and medically disadvantaged' (paragraph 8). The difficulties that can arise when meeting the requirement of comparing a new treatment to the best current method of treatment while also recognising the needs of the economically and medically disadvantaged are discussed below.

Table 7.1

Primary sources of international guidance on standards of care

Source	Text
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)[1]	Research in developing countries should be 'responsive to the health needs and the priorities of the community in which it is to be carried out'. **Guideline 8** 'If there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified'. **Commentary on Guideline 14**
WHO 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	'The investigator is responsible for adequate and safe medical care (or dental care, where appropriate) of subjects during the trial ...' **Principle 4.1** 'In accordance with Sections 4.1 and 4.3 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality'. **Principle 7.1**
International Conference on Harmonization (ICH) Harmonised Tripartite Guideline. Guideline for Good Clinical Practice (1996)	'Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)'. **Principle 2.1** 'During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events ... related to the trial'. **Principle 4.3.2**
World Medical Association 'Declaration of Helsinki' (2000)	'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods.' **Paragraph 29** 'Even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.' **Paragraph 6** 'The particular needs of the economically and medically disadvantaged must be recognised'. **Paragraph 8**
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	'As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial'. **Guidance Point 11** 'Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of ... circumstances listed.'[2] **Guidance Point 16**

[1]This guidance is currently being modified and the revised edition is expected to be published in 2002.
[2]Circumstances include: level of care and treatment available in the sponsor country, highest level of care available in the host country, highest level of treatment available in the host country (including the availability of antiretroviral therapy outside the research context in the host country), availability of infrastructure to provide care and treatment in the context of research, potential duration and sustainability of care and treatment for the trial participant.

Defining the best current method of treatment

7.4 When considering what the Helsinki Declaration requires, a clear understanding of the complexities of defining 'best current' method of treatment is needed. One definition of the best current method for a particular disease might be that which is most effective. However, achieving agreement about the most effective method is often far from straightforward. First, there may be a divergence of views within a particular medical community about what constitutes the best method of treatment. Even the evidence from controlled trials may be inconclusive or subject to debate, leaving scope for disagreement about which method of intervention is the 'best'. Secondly, even if one medical community reaches a consensus about what constitutes the best current method of treatment, there may be disagreements among different medical communities. For example, the UK and US have different views about the methods used to screen for lung cancer (see Box 7.2).

7.5 Although there may be some debate about what constitutes the best current method of treatment available anywhere in the world, there is usually less room for debate about which is the better

when comparing the methods available in developing countries as against developed countries. Because of the greater resources available, in many instances it will be unarguable that the care available in developed countries for a particular condition is better, i.e. more effective, than that widely available in a developing country. In light of this disparity, the issue we address is what standard of care should be provided to participants in research when there is a discrepancy in the standard of care in the country in which the research is conducted and the country sponsoring the research.

BOX 7.2 Screening for lung cancer

At present a trial is being planned in the UK and other European countries to determine whether a novel form of screening for lung cancer will reduce mortality by detecting the cancer. In the trial, one group will receive the new form of screening (low dose spiral computed tomography), while the control group will receive no screening. In a similar trial planned in the US, this new form of screening will be compared to screening using a chest x-ray. In contrast to the US, the view held in the UK, and in some other European countries, is that there is no evidence that a chest x-ray is an effective method of screening.

The appropriate standard of care for control groups in clinical trials

7.6 The different approaches that have been proposed when deciding the level of care that should be provided for those in the control group of a clinical trial can be divided into two broad categories:

- universal: the best treatment available anywhere in the world, wherever the research is conducted
- non-universal: the treatment available in a defined region.

Our aim in making this distinction is to separate the universal or global 'best' from all other levels of care, be they local, regional or national.

7.7 The approach of those who are in favour of a universal standard of care being provided to the control group in clinical trials is set out in a widely quoted editorial by Marcia Angell in the **New England Journal of Medicine**:

> I believe that our ethical standards should not depend on where the research is performed ... Furthermore I believe the nature of investigators' responsibility for the welfare of their subjects should not be influenced by the political and economic conditions of the region. It would follow that these conditions should not be used to justify providing a lower standard of care for some subjects than they would have received had they taken part in the same study in a different place. In practical terms any other position could lead to the exploitation of people in developing countries, in order to conduct research that could not be performed in the sponsoring countries.[1]

7.8 Marcia Angell sets out at least three principles: one concerned with the importance of avoiding the exploitation of people in developing countries; one concerned with the responsibilities of researchers and sponsors or research; and one concerned with the need to avoid making the standard of care depend upon the local context. We address each of these in turn.

1 Angell M (2000) Investigators' responsibilities for human subjects in developing countries, **New England Journal of Medicine**, 342(13) 967–9.

Avoiding exploitation

7.9 The Working Party is firmly of the view that the need to avoid exploitation is imperative. As we have stated in Chapter 4, it is a fundamental ethical principle that those involved in research in developing countries, including research teams, pharmaceutical companies and governments, should not take advantage of the vulnerabilities created by poverty or a lack of infrastructure and resources. However, as discussed below, the Working Party considers that insisting upon a universal standard of care may not always be the best way to respect this principle.

7.10 At first sight, justice might seem to require that we treat people identically, regardless of context, because justice demands equal respect. If showing respect for the participants in a particular research project in the developed world demands that they receive a particular intervention, it would seem to follow that parity of respect means that participants in similar research conducted in the developing world should receive the same intervention. To apply a lower standard of care would thus be not only to take advantage of the participants' vulnerabilities, but also to commit an additional wrong by perpetuating an injustice. However, the principle of equal respect does not imply that we must behave towards others in a uniform manner, since features of individuals and of their circumstances will differ. Parity of respect requires us to address the specific needs and circumstances of individuals in determining how to behave towards them. What we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a [relevant] reason should be given'.[2] Thus, the context of the research in different countries must be critically assessed to establish whether or not it provides a morally relevant reason for offering a different standard of care (see paragraphs 7.17–7.18).

Responsibilities of researchers and sponsors

7.11 The goal of research related to healthcare is to gain information about diseases and to discover better methods of prevention, diagnosis and therapy that can be applied to benefit the wider community. Raising the quality of healthcare available to those in developing countries to the standard that exists in developed countries is necessarily a long-term goal. Given current inequities, it will clearly not be possible, in the short term, to improve the health of their populations to the level of their counterparts in the developed world. Research on improving preventive and therapeutic methods in developing countries is necessarily conducted within this context.

7.12 Some commentators have argued that by failing to extend to those participating in research in a developing country, the level of treatment that would be given in the sponsors' own, more wealthy country, external sponsors thereby harm the participants in research. Indeed, a central argument against the perinatal HIV-transmission trial (see Box 1.2) put forward by Lurie and Wolfe was that the conduct of the research would 'lead to hundreds of preventable HIV infections in infants'.[3] One response to this argument is to suggest that in not providing a universal standard of care, research sponsors do not harm the participants, they merely fail to benefit them; that is, they do not put participants in a worse position, but neither do they improve their position. However, this cannot be the end of the matter.

7.13 The fundamental duty to alleviate suffering has a natural extension, namely a duty to provide a positive benefit, though defining the extent of the duty to benefit in a given situation is a

2 See Williams B (1973) The Idea of Equality, in Williams B **Problems of the Self**, Cambridge University Press, New York, for a clear exposition of the view that what we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a reason should be given' that is relevant.

3 Lurie P and Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, **New England Journal of Medicine**, 337: 853–6.

challenging task.[4] In many research projects, it will be the case that the greater wealth of the sponsoring country or institution means that there will not be a financial barrier to offering a higher level of care than that which is available locally to those in a specific research study. The Working Party notes that a person's duty to benefit another is related to his or her capacity to do so, whether financial or practical. If a particular benefit cannot be provided for reasons of practical constraint, the duty to do so is weakened. Conversely, if a country's wealth allows it to confer a benefit on the inhabitants of another country when that country cannot do so itself, the wealthier country has a stronger duty to provide that benefit.

7.14 In some research projects, the care provided to participants in developing countries can be higher than the national standard without significantly affecting the requirement to conduct research relevant to that country's health needs or the economic constraints on sponsors. This is most likely to be the case with respect to the treatment of conditions that arise among participants in research during the course of a study. For example, consider a trial of a new vaccine for malaria that is conducted in an area where there are high levels of drug-resistance to the disease. The main aim of the research may be a comparison of the incidence of malaria in the two arms of the trial (new vaccine and control), but researchers may be able to make available medicines that may not be available nationally for the treatment of cases of malaria. However, the desirability and sustainability of such measures should be fully discussed with local health services in advance, to ensure that the otherwise unavailable treatment does not lapse as soon as the research is completed (see Chapter 9).

7.15 It must be noted, nonetheless, that the most effective way to discharge the duty to alleviate suffering with respect to a particular research participant will not necessarily be to provide them with a universal standard of care during the conduct of research. For example, patients with chronic diseases may not be better off in the long term if they receive a standard of care during a research project which cannot be sustained once the project ends. In other words, the question of what standard of care and treatment should be made available during the conduct of research may not be separable from the question of what care is made available once the research is completed. Should participants require long-term care, the two issues necessarily overlap.

Unsafe practices

7.16 Researchers will be obliged to raise the standard of care above the national standard when that national standard is unsafe. In the example from South-East Asia set out in Box 7.3, the re-use of equipment for taking blood was the routine local practice. Researchers have a duty to prevent avoidable harm to participants in research. The use of unsafe or harmful practices, even if they

BOX 7.3 Research in South-East Asia

Research studies in one South-East Asian country required a lancet to be used to take a blood sample. In that country it was common practice for lancets to be re-used after being dipped in alcohol. In most countries, lancets are not re-used because of the high risk of cross-infection. Health professionals in the country were aware of the risks inherent in the multiple use of lancets, but a period of famine had just ended and there were very limited financial resources to purchase new equipment. Researchers wanted disposable lancets to be used in the study. To avoid creating internal difficulties within the hospital, it was therefore necessary to provide an adequate supply of such lancets for the whole of the hospital.[1]

1 Personal communication, Working Party fact-finding meeting.

4 For a thought-provoking attempt to set out the limits of this obligation, see Unger P (1996) **Living High & Letting Die: our illusion of innocence**, Oxford University Press, New York.

are routine locally, is unacceptable. It follows that adopting a non-universal rather than a universal standard of care in research does not provide a justification for employing unsafe practices.

The importance of the research context

7.17 In paragraph 7.10 we noted that equal respect for participants in research does not necessarily entail that they should receive equal treatment, regardless of where the research may be conducted. Instead, the circumstances in which the research will be conducted must be critically assessed to establish whether or not the variations in circumstances provide a morally relevant reason for offering a different standard of care.

7.18 We take the view that, in determining the appropriate standard of care to be provided to participants in the control group of a research trial, a number of factors should be considered by sponsors, researchers, and research ethics committees. These include:

- the appropriate research design(s) to answer the research question; (in some situations only one research design may be appropriate to answer the research question, in others a number of research designs, in which different standards of care are offered to the control group, may be possible)
- the seriousness of the disease and the effect of proven treatments
- the existence of a universal standard of care for the disease or condition in question and the quality of the supporting evidence
- the standard(s) of care in the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can be afforded by the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can effectively be delivered in the host country(ies) during research
- the standard(s) of care which can be provided in the host country(ies) on a sustainable basis.

7.19 Taking the above considerations into account, in some circumstances, it will be clear that a control group in a clinical trial should receive a universal standard of care, wherever they live (see Box 7.4). For example, if research were to be conducted in any developing country into a new treatment for schistosomiasis, we consider that the control group in such research should at least be offered praziquantel or a medicine with the same efficacy. We base this view on the fact that an effective, proven treatment for schistosomiasis exists and has been approved and implemented in affected countries around the world. The treatment has been demonstrated to be affordable and feasible to deliver, in a sustained manner in developing countries. Any future research is likely to focus on forms of care that are better than this treatment, and thus it will be an appropriate comparison for the control group to receive.

BOX 7.4 Treatment of schistosomiasis with praziquantel

For some diseases there is widespread agreement about the standard of care that will be provided for those infected, wherever they are in the world. For example, cost-effective control tools, based on treatment with praziquantel, are available for treating schistosomiasis. This has resulted in prolonged, sustainable national control programmes in endemic countries such as Brazil, China, the Philippines and Egypt, and eradication or near eradication of the disease in countries such as Puerto Rico, Venezuela, Saudi Arabia, Tunisia and Morocco. Africa now accounts for an estimated 80% of the remaining cases of the disease and WHO is committed to reviving control of the disease in Africa, with a simple morbidity control package including affordable access to praziquantel at all levels of healthcare.[1]

1 See http://www.who.int/ctd/schisto/index.html.

7.20 In contrast to the case above, there are situations in which it is clear than even if there were an agreed universal standard of care for a disease, it may not be possible for this standard to be provided to the control group in a research project. In some cases the universal standard of care will not be able to be provided because of practical considerations. For example, if a treatment was sought for a condition such as liver cancer (which often develops in carriers of hepatitis), the universal standard of care includes surgery to remove the tumour or a liver transplant. While the sophisticated infrastructure required to provide such treatments is available in developed countries, (including intensive care units, trained surgeons and healthcare staff) it is very limited or absent in the majority of developing countries. If researchers sought to develop a form of treatment for liver cancer which would be affordable, deliverable and sustainable in developing countries, it is unlikely that it would be possible to provide a universal standard of care to the control group in the research.

7.21 Practical constraints may not be the only factor preventing delivery of a universal standard of care in research. For example, when research into preventing the perinatal transmission of HIV was conducted in the Cote d'Ivoire in 1995, researchers were not able to provide women in the control group with the universal standard of care which involved administration of the medication in pregnancy, intravenous infusion during labour and delivery, and administration of the medicine to the infant four times a day for six weeks. This complicated regimen, which requires voluntary counselling and testing for HIV to be performed early in pregnancy, has limited application for many developing countries where women have poor access to antenatal care and may only seek assistance from healthcare workers after the onset of labour.

7.22 In the two cases outlined above, even though a universal standard of care cannot be provided to participants, it can be convincingly argued that the research should nevertheless be conducted because it offers the opportunity of developing responses to important healthcare needs in developing countries.

7.23 We have set out contrasting cases in which it can be said to be respectively appropriate or inappropriate, to offer a universal standard of care to participants who are in control groups. However, the decision about whether or not a universal standard of care is called for is usually not so straightforward. It involves a careful consideration of the various factors outlined in paragraph 7.18. In circumstances where it is apparent that a universal standard of care is not appropriate, further analysis of these factors will be required to determine what the appropriate standard of care should be.

7.24 In some circumstances, differing research designs may each provide relevant information about a particular disease or intervention. Researchers and research ethics committees will need, therefore, to consider which design is the most suitable. A number of respondents to our public consultation and in our fact-finding meetings stressed the importance of involving local researchers when designing research and determining appropriate standards of care. An awareness of the standards of care currently being used within developing country(ies) and of information sought by local providers of healthcare will increase the likelihood of research being relevant to local needs and producing results that are likely to be applicable in developing countries.

7.25 It should be borne in mind that any definition of the 'best treatment' which may be available in a country is subject to change over time, in response to the results of research, and will affect the standard of care that it is appropriate to offer to participants in research. For example, in initial trials investigating perinatal HIV transmission in Thailand which involved testing a short course of therapy (see Box 1.2), a trial design in which the control group received a placebo was considered to be acceptable. Since this research has demonstrated the effectiveness and feasibility of the short course treatment in Thailand, further research which provides the control

group in the research project with anything less than the short course of treatment would be unethical. Currently, trials to assess the potential additional efficacy of new medicines or combinations of medicines in preventing perinatal transmission of HIV in a developing country setting provide a short course regimen of proven efficacy to the control group.[5]

Defining a non-universal standard of care

7.26 Where it is not appropriate to require that a universal standard of care be provided to the control group, in the light of all the relevant circumstances, questions arise about what standard of care should be provided. For example, should it be a national, regional or local standard? Should it be the level of care available in a local hospital, a district hospital, tertiary institution or within the private sector? The ultimate goal of research must be to provide information about treatment and other interventions which can then be used by national governments to ensure that improvements are made in the provision of healthcare. Thus, for policy reasons, it seems sensible to take the particular country as the unit of focus, as it is national governments which, by and large, take responsibility for the health of their citizens and which make decisions about the provision of healthcare. With knowledge of the resources available to them, governments make decisions about the level of care which they can provide for the prevention and treatment of specific diseases or conditions. In that context, they set targets for the level of care that they will strive to achieve, often recognising that it will not be possible to meet this goal.

7.27 The Working Party is of the view that in externally-sponsored research, the level of care that ought to be offered to participants should, as a minimum, be the standard that the country endeavours to provide nationally. In many circumstances, it may be appropriate for researchers to offer a higher level of care than this, while still conducting research that is relevant to the local setting. Exceptionally, it may be appropriate to provide a level of care that falls below the national standard. The ethical justification for this, however, will need to be carefully argued and accepted by local authorities and ethical review bodies before such research can be conducted (see paragraph 7.30).

7.28 We have previously noted that defining the 'best treatment' is not straightforward (see paragraphs 7.4–7.5, 7.25). Similarly, it may not be easy to identify a single 'national standard' of care. In many countries, the 'best' levels of care may be available within private healthcare systems, although in most developing countries these provide care for only a small proportion of the population, while most people are served by the public health service. In setting the national standard of care, it would seem appropriate to concentrate on what can be provided within the public health system, as this is under the direct control of national governments. The challenge in defining the national standard of care may be greater in large countries (with regional differences in access to healthcare) than in small countries. In some circumstances it may be appropriate to use a regional standard (within a country) rather than the national standard. However, again this will need to be carefully justified.

7.29 We conclude that discussion with clinicians, researchers and representatives of government and health authorities within the host country is essential so as to establish what the best national level of treatment available as part of the national public health system is. **We recommend that in setting the standard of care for the control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a**

5 For example a study in South Africa is comparing the efficacy of two new medicines alone, and in combination with a zidovudine only short course regimen.

universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system. A summary of the reasoning behind this conclusion is given in the Box 7.5.

Deviations from the national standard

7.30 In exceptional circumstances, research may be proposed which involves the use of a standard of care that is lower than the best available intervention as part of the host country's public health system for the disease being studied. For example, researchers may wish to demonstrate that what is deemed to be the best treatment available through the host country's public health system is ineffective, or even harmful, by comparing it to a placebo, or an apparently lesser standard of care. Alternatively, researchers may wish to show that the best available intervention in the host country as part of the public health system for a particular disease is so beneficial that it should be made more widely available within the country (see Box 7.6). Prophylactic chemotherapy to prevent tuberculosis (TB) is widely recognised to be the best treatment for individuals who are HIV positive in countries in which TB is endemic. However, it is not possible to provide this treatment in many African countries that can barely maintain their current TB Control Programmes. Research to investigate how to implement prophylaxis for TB might compare current practice (normally no prophylaxis) with other approaches. If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.

BOX 7.5 Summary of arguments about standards of care

The principle of not exploiting those who are vulnerable lends support to the adoption of a universal standard of care so that people in different countries receive the same care and treatment during research.

However, in some circumstances it may not be possible to adopt a universal standard of care. In other circumstances, providing a universal standard of care to the control group may not provide research results that are relevant to the country in which the research is conducted.

In an ideal world, variations in healthcare resources throughout the world would be eliminated. But the duty to undertake research requires us to act even in a non-ideal world where resources are limited and not equally distributed.

Therefore, the challenge is to fulfil this duty to undertake research in a way that is consistent with the principle of not exploiting those who are vulnerable.

This can be achieved by requiring the standard of care to be universal where possible, or at least that which is available as part of the national public health system of a country, and by improving standards wherever feasible.

BOX 7.6 STD and HIV research

In one country, a national programme for the treatment of sexually transmitted diseases (STDs) was not widely implemented, so that, in many regions, the availability of antibiotics to treat STDs, as contemplated in the programme, was limited. Research was conducted in which randomised communities received either existing care, or the antibiotic treatment for STDs recommended in the national programme. The rationale for this research was to demonstrate that if the national programme was widely available, it would reduce both the level of infection with STDs and HIV. Once this finding was demonstrated, the evidence that treating STDs would also reduce the level of HIV infection provided an incentive for the government to make the national programme for treating STDs widely available. The research also demonstrated that it was possible to implement the national programme on a large scale.[1]

1 Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Serkoo K *et al.* (1995) Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial, **The Lancet** 346(8974) 530–6.

7.31 Research on the management of outbreaks of disease in isolated places may necessarily involve standards of care that are lower than the best which are available nationally. For instance, research on the management of an outbreak of meningococcal meningitis in Northern Nigeria may have to accommodate thousands of people being cared for in the open, the performance of lumbar punctures and the administration of single-dose antibiotic therapy under conditions that are clearly less than the national standard. Denying these communities the opportunity to participate in research denies them improvements in healthcare and new ways to manage sick patients in settings with very limited resources.

Research into preventive measures

7.32 In some forms of research, such as those designed to determine the incidence of a disease in a population, or to prevent participants from contracting or developing a disease, the standard of care received by participants who develop the disease will not be immediately relevant to the research.[6] This is because the research is focused on preventing participants from contracting the disease, rather than the subsequent effects of and possible treatments for the disease. Under these circumstances, however, there is still a need to consider the standard of care which a patient should receive because the disease, once diagnosed, may have serious implications for the individual. The issue was the subject of extensive consultation in the developing countries in which the research to develop a vaccine to prevent infection with HIV was to be undertaken. Following these consultations the UNAIDS guidance on ethical considerations in research on a HIV preventive vaccine recommends:

> Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial, taking into consideration the following:
>
> - Level of care and treatment available in the sponsor country
> - Highest level of care available in the host country
> - Highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country
> - Availability of infrastructure to provide care and treatment in the context of research
> - Potential duration and sustainability of care and treatment for the trial participant.
>
> **Guidance Point 16**[7]

7.33 **We endorse Guidance Point 16 of the UNAIDS guidance on Ethical Considerations in HIV Preventive Vaccine Research. We conclude that when research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease under study. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease.**

6 For example, in vaccine trials and studies of other measures to prevent diseases such as malaria and AIDS, research will be designed to test the effectiveness of the proposed intervention. This assessment can be made by determining how many of those who receive the intervention go on to develop the disease being studied.

7 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document**: Guidance Point 16.

Care for other conditions

7.34 During research into some diseases, participants may develop a condition that is related to the condition under study. For example, in certain regions individuals with STDs are more likely to become infected with HIV than those without (see Box 7.6). In addition, during research, participants may develop an entirely unrelated condition. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a local health centre where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system.

7.35 As discussed in paragraph 7.13, in addition to researchers' duty not to harm participants in research, there is a duty to benefit participants where possible. Thus, where it is feasible for researchers to diagnose and treat an illness which arises, or to ensure that effective treatment is available at a local level, they have a duty to do so. This is a complex issue and decisions will need to be made on a case-by-case basis following discussion with clinicians, researchers and representatives of government and health authorities within the host country. **We recommend that before research begins, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard deviation must be justified to the relevant research ethics committees.**

Chapter 8

Ethical review of research

Introduction

8.1 The requirement that the ethics of proposed research be reviewed (hereafter called ethical review) is designed to protect participants in research. The need for such review is now widely recognised and set out in national and international guidance (Table 8.1 and Appendix 1 Table 4). The research ethics committees which typically undertake such reviews are a relatively recent

Table 8.1

Primary sources of international guidance on reviewing the ethics of research

Guidance	Text
Council for International Organizations of Medical Sciences (CIOMS) 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	'The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals ... Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees. Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data. An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases ... Nevertheless, in such circumstances the investigator will ... respect the rights of individuals'. **Principle 33**
CIOMS 'International Ethical Guidelines for Biomedical Research involving Human Subjects' (1993)	'All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees. The investigator must obtain such approval of the proposal to conduct research before the research is begun'. The function of ethical review to protect participants whilst ensuring the quality of research is also elaborated: 'Scientific review and ethical review cannot be clearly separated: scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risk or inconvenience to no purpose'. **Guideline 14**
World Health Organization (WHO) 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	'The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations), review bodies ... constituted appropriately for this purpose and independent of the investigator(s) and sponsor'. **Paragraph 2** 'The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol ... and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects ... Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures'. **Paragraph 3.2** 'Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s)'. **Paragraph 4.9**
International Conference on Harmonization (ICH) 'Harmonised Tripartite Guideline. Guideline for Good Clinical Practice' (1996)	'A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion'. **Paragraph 2.6**
World Medical Association 'Declaration of Helsinki' (2000)	'The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval, to a specially appointed ethical review committee ...' **Paragraph 13**
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	'HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review'. **Guidance Point 6**
WHO 'Operational Guidelines for Ethics Committees that Review Biomedical Research' (2000)	'Countries, institutions, and communities should strive to develop Ethics Committees and ethical review systems that ensure the broadest possible coverage of protection for potential research participants and contribute to the highest attainable quality in the science and ethics of biomedical research. States should promote, as appropriate, the establishment of research ethics committees that are independent, multidisciplinary, multi-sectoral, and pluralistic in nature. Research ethics committees require administrative and financial support'. **Paragraph 3**

innovation (for example, the first committee in the UK was established in 1966).[1] Committees with responsibility for reviewing the ethics of research now exist in most countries.

Levels of assessment

8.2 The Working Party considers that each proposal for externally-sponsored research in developing countries should receive three levels of assessment:

- relevance to priorities in healthcare within the country(ies)
- scientific validity
- ethical acceptability.

In this chapter, we briefly discuss assessment of the relevance of the research to priorities in healthcare and the scientific review of research, and then focus on ethical review of research. A list of questions that may be relevant during these three forms of review is set out in Appendix 3.

Relevance to priorities in healthcare

8.3 Research ethics committees are not constituted to take policy decisions on, for example, whether the findings of a research project could be implemented in the country. We consider that they should, however, determine if the implications of the possible research results have been considered, including the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (see paragraphs 9.32–36). In addition they should request justification for research that does not include provisions for the development of expertise in research within the developing country (see paragraphs 9.50–52).

Scientific review

8.4 Rigorous scientific evaluation of each research protocol is essential. Research which is not appropriately designed will fail to provide answers to the question posed by the research, and thus have limited benefit or no benefit either to the participants, or to the wider community. Some sponsors of research conduct their own scientific review of proposed research. However, these internal reviews cannot always be relied upon. Sponsors are often presented with proposals in outline from applicants that exclude many of the details essential to scientific review, such as the size of the sample of population and the specific definition of the study groups. Internal scientific reviews of proposed research undertaken by the pharmaceutical industry may be fully or partially confidential and therefore not comprehensively available to external review committees. Research ethics committees must be satisfied that appropriate scientific review of research has taken place.

8.5 There are concerns that, in a single ethics committee, the distinction between the review of the science and the ethics, which have quite different purposes, may be ill defined. We accept that it is not possible to entirely separate the processes of reviewing the science and the ethics of a research proposal. One depends to a degree on an appreciation of issues addressed by the other. Nevertheless, they should be undertaken as separate exercises. We conclude, therefore, that these two forms of review should, where possible, be kept separate. This may, but will not necessarily, require the establishment of separate committees.

1 Ferguson P (2001) Do researchers feel an LREC hinders research? **Bulletin of Medical Ethics**, 165 17–19.

Ethical review of research

8.6 An ethics committee's primary task is to review the ethical acceptability of research proposals. Particular attention is usually paid to:

- the *predictable* risks involved in conducting the research
- the anticipated benefits for the participants in research and communities to which the research will be relevant
- the provisions within the design of the research relating to the care and protection of participants in research, including the treatment of any participant harmed by the research
- the procedures for recruitment and selection of participants in research (including details of the group to be investigated)
- the processes for obtaining genuine consent and provision for refusing consent or withdrawing it during research (including the adequacy of information given to participants and the acceptability of any inducements)
- the provisions for protecting the security and confidentiality of data about patients.

8.7 In the preceding chapters and the following chapter, we have examined in detail a number of issues that need to be considered by research ethics committees when reviewing externally-sponsored research. These include the appropriateness of procedures for giving information about the research to prospective communities. For example, in Chapters 6 we noted that it was necessary to draw on the expertise of a local research ethics committee to ensure that procedures for consent enabled prospective participants in any research to give genuine consent, and that any inducements to participate were appropriate (see paragraphs 6.32, 6.40). In Chapter 7 we recommended that, rather than requiring that a universal standard of care should always be provided to a control group during a clinical trial, a decision should be made in each case on what would be the most appropriate level of care to be provided. Such decisions can only be made in consultation with local researchers and local research ethics committees (see paragraphs 7.18, 7.29) and should be made by reference to the reasons and argument we set out in Chapter 7. In Chapter 9 we endorse the US National Bioethics Advisory Committee (NBAC) recommendation that researchers should have to justify the lack of arrangements for securing post-trial access for effective interventions for participants in a trial to the ethics review committee (see paragraph 9.31). We also conclude that an ethics review committee would need to be persuaded of the need to carry out a study involving a novel intervention to treat chronic disease in a locality where the availability of long-term treatment is unlikely.

8.8 The mere presence of a research ethics committee in a country is not enough to ensure that research will be adequately reviewed. Committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience with, reviewing the ethics of research. In Box 8.1 the current capacity of a selection of countries to conduct such reviews is outlined.

Requirements for effective ethical review of research

8.9 As we have said, an effective system of ethical review is a crucial safeguard for participants in research. Research ethics committees are one component of a system for ensuring the protection of participants in research within a country. However, if there is little support for a system of ethical review amongst government officials, senior members of universities and research

BOX 8.1 Differing capacities to conduct ethical review

In some developing countries there are no research ethics committees. For example, Myanmar and Laos have no formal internal ethical review process for research related to healthcare.[1] Such countries may, however, have other mechanisms in place to provide a review of research, including the possibility of review by officials from the national Ministry of Health. In addition, a country without a committee may request a research ethics committee from neighbouring countries to review proposed research. For example, in Guinea Bissau, once the government has considered proposed research and decided that it is relevant, it is passed to the national ethics committee in The Gambia, for review.

In India, there are clear and robust guidelines for externally-sponsored research, as well as for nationally funded research (see Appendix 1 Table 1). In addition to the national research ethics committee, there are many local and institutional review committees.[2] The quality of assessment, however, varies among the local committees.[3]

In Latin American countries, regulatory procedures for the evaluation of new medicinal products generally require both local scientific approval, and approval by an independent ethics committee. In Argentina, a single ethics review committee can approve multi-centre studies for centres which do not have their own ethics review committee. In Brazil, the number of research projects which have been approved has grown from 30 in 1995 to 430 in 1999, and national regulation for the ethical review of research proposals has recently been established.[4] A federal resolution was approved in October 1996 by the National Council of Health, requiring that all research projects involving human participants receive ethical review.[5]

Research ethics procedures in Central and Eastern Europe vary greatly from one country to another, for largely historical reasons. Bulgaria, Hungary, Poland and Romania have national ethics committees as well as local ethics committees in hospitals. Albania and Lithuania have national ethics committees, while Estonia has two research ethics committees, in addition to a bioethics council and an ethics committee related to the planned Estonian Genome Project. The Czech Republic has institutional ethics committees while Russia has a committee in the Ministry of Health and another in the Academy of Medical Science: both are currently developing guidelines but are not yet reviewing research proposals. There is also a regional research committee in St. Petersburg. The Ukraine until recently has had no research ethics review system, and preparatory work here and in other Eastern European countries is supported by the Council of Europe.[6]

1 White N (2000) Personal communication, Wellcome – Mahidol University – Oxford Tropical Medicine Research Programme.
2 The ethical guidelines and the National Research Ethics Committee are the responsibility of the Indian Council of Medical Research, which had a budget of nearly US$50 million in 1999–2000.
3 Personal communication, Working Party fact-finding meeting.
4 Brasil, Decreto 98 830, 15 Janeiro 1990 (Coleta por estrangeiros de dados e materiais cientificos no Brasil).
5 The resolution sets out the terms of reference for the establishment and operation of ethics review boards and the creation of the Central Committee of Ethics in Clinical Research (CONEP) as an adjunct to the Ministry of Health. Research ethics committees must report to CONEP on a quarterly basis about the status of trials of new products.
6 Coker R and McKee M (2001) Ethical approval for health research in central and eastern Europe: an international survey, **Clinical Medicine**, 1(3) 197–9.

institutions, or local researchers, then research committees may not be established, or may be unable to function effectively due to a lack of training and resources, or a lack of independence. In some instances, researchers may submit research for approval in developing countries, only to have it 'approved' within a few days, with no amendments or changes proposed.[2] Under these circumstances concerns have been expressed that officials in developing countries do not recognise the need for effective ethical review and consider it to be simply a formality. Alternatively, the decisions of the research ethics committees may be ignored or overridden by government officials.

8.10 Furthermore, if a committee has limited independence and no clear framework of guidance to work within, there is a danger that they may take *ad hoc* rather than principled decisions, and

2 Melody Lin (2001) Personal communication, Office for Human Research Protections, US.

that these *ad hoc* decisions may reflect members' affiliations and interests, and pressure from host and foreign researchers, sponsors and local government or other administrative authorities. For example, a research ethics committee might find it difficult to refuse research that it considered inappropriate but which would bring a substantial funding to an institution or region. As we have said in paragraphs 5.25 and 5.28, the guidance on research related to healthcare can be ambiguous and difficult to apply in specific circumstances. For this reason we encourage countries to create national guidance for the clear and unambiguous application of existing international and national guidance. The need to provide training for members of research ethics committees so that they can act effectively is discussed below (paragraphs 8.26–8.29).

8.11 The membership of research ethics committees requires careful consideration. The aim must be to achieve an independent, multi-disciplinary, efficient committee with sufficient expertise. Recent guidance from international bodies on the membership of research ethics committees is set out in Appendix 1 Table 4. With regard to attendance, in order to ensure that meetings are quorate, it is helpful to have more members than are required for a quorum. In the case of renewal of the membership, it is helpful to maintain a rotation of new members, not least because they inevitably take time to learn about the process of ethical review. We note that the inclusion of representatives of relevant religions may present difficulties if there are several religions represented within the host community. However, many theological scholars have given substantial thought to issues that need to be considered by ethics committees and their participation may be particularly valuable.

8.12 In some countries, it is considered an advantage to have a majority of members in a research ethics committee who are not professionals in the various fields covered by research (sometimes referred to as lay members).[3] Their primary role is to reflect the values of the local communities and the local and national culture. Particular care will need to be taken to ensure that the interests of women and members of vulnerable populations are properly taken account of by research ethics committees. In countries which do not have research ethics committees, members of a committee from a neighbouring or sponsoring country may well have an incomplete understanding of the local conditions in the host country. As a consequence, any review may be inadequate. Moreover the geographical and social isolation from the communities under study may make any monitoring of the research difficult.

8.13 The independence of members of ethics committees is a common problem. In many developing countries, members of research ethics committees may not be able to afford to provide the necessary time and expertise to review research at no cost. Failure to provide appropriate remuneration may contribute to delay or to inadequate reviews. However, when committee members receive a fee for review, their independence may be compromised.

8.14 In many developing countries, there is often a limited number of people available who have the expertise and the time and who are able to bring to bear the kind of knowledge and care required to act as effective members of a research ethics committee. One example cited to the Working Party concerned the directors of two institutes who were members of each other's ethics committees, leading to a possible conflict of interest.[4] Moreover, prospective reviewers with the appropriate scientific background may in fact be involved in the research, creating a potential conflict of interest. Where conflicts of interest are unavoidable, the procedures for managing them should be transparent, and may include the requirement that the conflict be declared and that a member be excluded from discussions when appropriate.

3 Lay members are individuals who represent a range of community and cultural values (and are not members of the specialist professions represented on research ethics committees, such as physicians, scientists, nurses and ethicists).

4 Das PK (2000) Personal communication, Vector Control Research Centre (VCRC), India.

8.15 Some research ethics committees meet infrequently, or at irregular intervals, which will delay review of research protocols. For example, if a committee meets only three or four times a year, a backlog of research proposals may build up. In some situations, sufficient funding will allow research ethics committees to meet more regularly, while in others, delays caused by a lack of infrastructure, for example difficulties of travel, may be more difficult to overcome.

8.16 **We recommend that all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.** Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. **In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level.**

Meeting the costs of research ethics committees

8.17 In developing countries, research ethics committees may have access to only limited administrative or financial support. Recent estimates suggest that the operating costs of one research ethics committee in the UK are £36,000 per annum, if both direct and indirect costs (such as time taken by committee members for review) are taken into account.[5] This does not include start-up costs, reimbursement of costs of travel, costs of interacting with other committees, or of monitoring and evaluating approved projects. In the US, ethics review committees may cost up to US$500,000 per annum to support.[6] While the costs of running research ethics committees in developing countries will be much lower, such costs still represent a significant burden on limited resources.

8.18 To meet the financial costs, some research ethics committees receive regular funding from government. Others levy fees for reviewing research protocols. For example, in the UK, the Oxford regional research ethics committee charges pharmaceutical companies to conduct a review.[7] Research ethics committees may charge a set fee for review or a variable fee, based on a proportion of the proposed research budget. While external sponsors generally recognise that set fees for reviewing research are a legitimate overhead cost, and some are encouraging such costs to be clearly identified in funding applications, they are often less willing to pay a proportion of the research budget for such review, particularly when this amounts to a significant sum.

8.19 Research ethics committees that levy fees may find it difficult to maintain their independence if fees are paid to the committee directly, rather than into a central fund, which can then be used for such matters as developing infrastructure, training and development for such committees. This possible weakening of independence may be the case even though the funds are intended for logistical support of the effective functioning of the committee. To meet this concern, in countries in which there is no central pool into which such levies may be paid, they could be paid to a local or national government and earmarked for support of research ethics committees.

8.20 Regardless of whether the financial support for research ethics committees comes from government, research institutions or as a result of levying fees for review, it is crucial that the independence of research ethics committees be maintained. **We conclude that there is a**

5 Squire SB (2001) Personal communication, Liverpool School of Tropical Medicine.
6 Wikler D (2000) Personal communication, World Health Organization.
7 Personal communication, Working Party fact-finding meeting in Oxford.

need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research.

8.21 The activities of research ethics committees need not be confined to approving or rejecting proposals for research. They may also play an educational or advisory role by suggesting modifications to proposals that are consistent with ethical requirements. In addition, research ethics committees should ideally play some supervisory or monitoring role once projects have begun. If unable to do so, an alternative is to appoint an independent monitor (for example a clinician), to monitor compliance with the agreed protocol and to ensure that the participants in the research project are suitably protected, but funding would need to be made available for this. In our view, it is highly desirable that research ethics committees throughout the world should request annual reports of progress from researchers. However, we recognise that many research ethics committees in both developed and developing countries do not currently have the resources to undertake such reviews. Therefore, we urge sponsors to allocate appropriate additional resources so as to facilitate the conduct of an annual review of research.

Reviewing research in the sponsoring country and the country in which the research is conducted

8.22 In order to ensure that acceptable ethical standards are observed in externally-sponsored research, research should be approved through a system of ethical review of research in both the host and the sponsoring country. As regards the latter, if a sponsor provides funding, it must have the means of ensuring that the funds are being used in a manner that is ethically acceptable. However, the country in which the research is to be conducted must also be satisfied about the ethical acceptability of the research. **We recommend that externally-sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted.**

8.23 The imbalance in power resulting from inequalities in resources discussed in Chapter 4 may extend to relationships between research sponsors, researchers and research ethics committees in developed countries on the one hand, and research ethics committees in developing countries on the other. For example, commercial pressures may be applied to committees in developing countries to use the same structures and procedures for ethical review as in the sponsoring countries. Guidance on research ethics committees in fact sets out a number of possible structures for such committees (Appendix 1 Table 4). Developing countries should, therefore, be able to adopt the structure(s) for research ethics committees that they consider will allow them to provide effective ethical review.

8.24 Difficulties may also arise when research ethics committees in developing countries are asked to review research before it is reviewed in the country of the sponsor. This may cause committees in developing countries to employ scarce resources to review research that the sponsor subsequently decides not to fund. On the other hand, once research has been reviewed in the sponsor's country, some research ethics committees in developing countries may be placed under pressure to concur with the opinion of the committee in the sponsor's country, particularly when reviewing forms of research of which they have limited experience.

8.25 Should there be disagreement between committees in the developed and developing country(ies), negotiation between the committees may be required. There should be mechanisms available to

facilitate such negotiation. At present such mechanisms, which are likely to benefit both host and sponsoring research ethics committees, are rare. Where there are irreconcilable differences between research ethics committees, a committee may choose not to approve the research. If a committee from a sponsoring country does not approve the research, the sponsor cannot fund it. If a research ethics committee from a developing country does not approve the research, then the research cannot be conducted within that country.

Developing capacity for reviewing the ethics of research

8.26 For research ethics committees to function effectively, committee members must receive adequate training. As many research ethics committees in developing countries have a rapid turnover of staff, regular training programmes for current and prospective members of committees are needed. A number of programmes are being established to develop expertise in the field of medical ethics and/or conducting ethical review. For example, the Fogarty International Centre of the National Institutes of Health (NIH) in the US is currently sponsoring training programmes in bioethics for faculties from developing countries. Towards the end of 2002, The Wellcome Trust will launch a funding initiative to support research into ethical and social aspects of conducting biomedical research in developing countries.[8]

8.27 The United Nations Development Programme (UNDP)/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) is addressing the need to strengthen the procedures for ethical review of research in developing countries through the training of key individuals in major research institutions.[9] WHO's guidelines, which are available in Cambodian, English, French, German, Lao, Russian, Spanish, Thai, Turkish and Vietnamese, bring together previous recommendations concerning the minimum requirements for the proper functioning of ethics committees.[10] The guidelines are currently being used in a number of regional fora which have been established to support the development of expertise in reviewing the ethics of research (see Box 8.2). In addition, regional workshops to train researchers and members of ethics review committees are currently conducted by the UNDP/United Nations Population Fund (UNFPA)/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

8.28 The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) is establishing networks within regions which will identify needs for training and education.[11] Each region has a forum, whose officers work with local governments, research institutions and participants in research and can represent the interests of research ethics committees at an international level (see Box 8.2).

8.29 Concerns have been expressed that training programmes for members of research ethics committees in developing countries, sponsored by a single developed country, may tend to reflect the views and procedures of the sponsoring country. **We recommend that international**

8 The majority of the research will take place in developing country locations where clinical or community oriented biomedical research is being done. An aim is to build capacity within developing countries to address ethical and social questions, and to increase the number of people with experience and training in this area.

9 Issues such as consent, standards of care and the protection of participants in research are part of a programme of training which also involves guidance on how to establish an effective research ethics committee.

10 World Health Organization (WHO) (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**, WHO, Geneva. These guidelines define the role and composition of an ethics committee, detailing the requirements for submitting an application for review. Emphasis is placed on maintaining global ethical standards, while taking into account local variations in practice.

11 SIDCER was developed with contributions from WHO, European Forum for Good Clinical Practice (EFGCP), industry and CIOMS in conjunction with other institutions and associations. SIDCER works in co-operation with the established regional fora for ethical review and the WHO Regional Offices.

programmes and organisations, including WHO, continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees. Funding should be provided to these international programmes for such purposes by bodies that sponsor research in developing countries.

BOX 8.2 Regional fora for developing the capacity for ethical review

A regional forum for ethics review committees in Asia and the Western Pacific (FERCAP) was established in January 2000. FERCAP has the objective of fostering an improved understanding and implementation of the ethical review of research by improving communication among ethics committees, acting as a collaborating centre and assisting in the implementation of relevant guidance. To date, it has sponsored a one-week training course in Bangkok in collaboration with a Thai and a Norwegian University.[1] Websites are being developed by FERCAP to assist in the dissemination of information. In addition to the regional fora, national bodies are being developed, for example FERCIT (the Forum for Ethical Review Committees in Thailand).

In Africa, a regional forum is being developed. PABIN (the Pan African Bioethics Initiative) aims to encourage the establishment of research ethics committees in countries in which they do not yet exist. It plans to conduct educational courses for members and potential members of research ethics committees in Africa.[2] The African Malaria Vaccine Testing Network (AMVTN) was set up in 1995 to assist in the planning and conduct of trials for a vaccine for malaria. It organises training courses in ethics for interested parties and will continue in this role, particularly while PABIN is developing.

In Russia and Eastern Europe, the Forum for Members of Ethics Committees in the Confederation of Independent States (FECCIS) was established in 2001. FECCIS plans to support the establishment of national and regional systems of ethical review, translate and distribute WHO's guidelines[3] and develop training courses for medical students and research ethics committee members.[4]

Similar bodies have been set up in Latin America (The Latin American Forum of Ethics Committees in Health Research (FLACEIS)) and the Caribbean.

1 See FERCAP's objectives and activities at http://www.fercap.org/ and 'The ethics of biomedical research' in **TDR News**, No. 63 (October 2000) at http://www.who.int/tdr/publications/tdrnews/news63/ethics.htm.
2 Chintu C (2001) Personal communication, PABIN.
3 World Health Organization (WHO) (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**, WHO, Geneva.
4 The three-year plan for the Forum for Ethics Committees in the Confederation of Independent States (FECCIS) (2001–2003).

Chapter 9

What happens once research is over?

Introduction

9.1 Much of the debate about the ethical issues which arise in externally-sponsored research in developing countries has focused on the protection of the participants during the study. However, there are also important issues concerning the welfare of those who have participated in the research and of the wider community once the research is over. The subsequent provision of interventions shown by the research to be successful, and continuing the provision of healthcare to research participants and to the wider community, are complex issues which confront researchers, research sponsors and providers of health services. Uncertainty about whether an experimental intervention will in fact prove to be successful, or be affordable, and the difficulty of guaranteeing that it will be available in the long-term have discouraged research sponsors from making commitments to participants and the wider community prior to embarking on any research. What makes these issues particularly difficult to resolve is that the possibility of introducing an intervention that has been shown to reduce morbidity or mortality may depend on support from external sponsors, other than those sponsoring the research, as well as action by national governments.

9.2 Most prominent among these various issues is the extent, if at all, to which diagnostics, medicines, surgical procedures and vaccines shown to be efficacious in research will be made available in the developing country in which the research was conducted. Many have voiced the opinion that participants in research should be guaranteed access to interventions shown to be successful once the study is complete, and that to fail to do so is a form of exploitation which is ethically unacceptable (see paragraph 9.21). However, in some circumstances, the subsequent provision either of interventions shown to be successful or of a better standard of healthcare[1] to participants in research and especially to the wider community is not straightforward. The provision of new medicines or better healthcare is primarily the responsibility of national governments. Sponsors of research are not therefore in a position to make unilateral decisions at the start of a trial without appropriate consultation. Nor are researchers usually in a position to guarantee provision of a new intervention once they have demonstrated its efficacy and safety. However, they may and frequently do act as advocates for the provision of a medicine or vaccine shown to be successful.

9.3 The main purpose of conducting clinical trials is to evaluate interventions that may be applied in the wider community, of which the participants in the trial are but a sample. While this may be true in general terms, there are often significant obstacles to the application of this principle in developing countries. A new or improved treatment may be expensive. If it is, the health authorities in an economically disadvantaged country are unlikely to be able to afford its distribution to the wider population. Researchers and sponsors must understand this and justify their decision to conduct research notwithstanding, if they wish to avoid the charge of exploitation.

9.4 Where a form of treatment which has been developed through research proves too expensive to be provided through the local healthcare system, what, then, are the responsibilities of the researchers and their sponsors? In particular, do they have any responsibility for ensuring that it is made more widely available after its efficacy has been demonstrated in a research study? Equally, if the provision of healthcare generally for participants has been improved during the study for the purpose of carrying out the research, is there a duty to maintain this level of healthcare after the research is over and, if so, on whom should such a responsibility fall?

9.5 What happens once research is completed will closely reflect how the research was conducted and in what context. The health and social conditions of those participating in the research, and the standards of care provided to participants during the study are relevant to what should be

1 i.e. better than the local standard.

provided for either these participants or the wider population at the completion of the study. When it is proposed to conduct clinical research in developing countries, the normal processes of review focus on the scientific merits and the ethical acceptability of the study. In addition, however, there is a growing consensus that the review of research should also address the issues that arise once the research is concluded.

9.6 While national and international guidance address some of these issues, the general nature of much of the guidance limits its usefulness to researchers or sponsors (Table 9.1 and Appendix 1 Table 5).

Table 9.1

International guidance on provision of healthcare after the research is over and the development of national expertise

Source	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	'Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities ... Research protocols should include provision for communicating such information to communities and individuals.' **Principle 13** 'While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.' **Principle 17**
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)	'As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified ...' **Commentary on Guideline 8** 'An ... objective of externally sponsored collaborative research is to help develop the host country's capacity to carry out similar research projects independently, including their ethical review ... external sponsors are expected to employ and, if necessary, train local individuals to function as investigators, research assistants, or data managers or in other similar capacities. When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited. Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy'. **Commentary on Guideline 15** 'Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study.' **Commentary on Guideline 15** 'The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available ... after the research, to the community from which the subjects are drawn and to the host country'. **Commentary on Guideline 15**
WHO 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	'The investigator is responsible for ... ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made'. **Paragraph 4.1**
World Medical Association 'Declaration of Helsinki' (2000)	'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' **Paragraph 30**
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	'Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.' **Guidance Point 2** 'Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process'. **Guidance Point 3**

For example, while the revised Helsinki Declaration (2000) refers to the need to provide those who participated in the research with access to the interventions developed during the research, and the CIOMS 1993 Guidance (Guideline 8) refers to the need to make any product developed reasonably available to the underdeveloped community in which the research is conducted, the complexity of the issues warrants further consideration.[2] National guidance from countries such as South Africa and Uganda also tends to be framed in general terms.[3] The US National Bioethics Advisory Committee (NBAC), however, in its report on clinical trials in developing countries, acknowledged implicitly the difficulties of making general recommendations to meet the needs of highly diverse situations.[4] In this chapter we therefore consider the issues raised and discuss how they might be resolved. They are in turn:

- the continued provision of a higher level of healthcare
- the benefits to individual participants and to the wider community arising as a consequence of the research
- the availability of an intervention shown to be successful once the research is concluded
- the long-term safety of an intervention
- the responsibilities of sponsors of research to contribute to the development of national expertise in research.

The continuation of improvements in healthcare

9.7 Participants in research related to healthcare usually benefit from their participation in the research, even if they are in the control group. This may be especially the case in studies conducted in developing countries with poorly funded healthcare services, for it is often necessary to improve the local health-care system for the purposes of conducting research. For example, improved diagnostic facilities may have to be introduced to permit reliable diagnosis of the disease(s) being studied. The need for repeated clinical observations may require regular visits to a physician. Not only may this expose the participant to improved healthcare; a further consequence may be that other conditions from which a participant suffers may be diagnosed and treated even though these are unrelated to the specific research.

9.8 The provision of a better standard of healthcare may be particularly significant when the research is conducted with the prime objective of advancing scientific and medical knowledge without there being any immediate benefit or risk to the individuals or the community involved in the study. For example, research into the development of a vaccine may require knowledge to be gained of how individuals' immune systems respond to a naturally occurring infection. Such immunological studies are unlikely to be of immediate benefit to the participants in the research, and therefore particular value may be placed by the local participants on any improvements in healthcare that are provided as part of the study. Indeed, the provision of better healthcare may form part of the inducement to participate in research (see paragraphs 6.29–6.30).

2 World Medical Association (WMA) (2000) **Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects**, adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. CIOMS (2001) **Draft Revision of the 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS**, Geneva.

3 See National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda and South African Department of Health (2000) **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa**.

4 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**, NBAC, Bethesda, Maryland.

9.9 Where research studies are on a large scale, the benefits of improved healthcare provided during the research may extend to the whole community, including those not directly involved in the research. Careful attention needs to be given to how such benefits are integrated into existing healthcare. For example, it may be necessary to improve the referral systems and diagnostic facilities at outlying centres. Alternatively, routine programmes of immunisation may need to be strengthened before trials of vaccines can be conducted.

9.10 During the study, the researchers can contribute directly to the strengthening of local healthcare facilities. In making such a contribution, however, careful consideration needs to be given to how sustainable any changes and improvements introduced for the purposes of the research might be. This is because any improvements are usually financed out of the research funds and, thus, may not be sustained once the research is completed. Much ill-feeling may be generated, and further research in the particular community compromised, if, at the end of the study, the researchers leave and the improvements to healthcare are not sustained much beyond the end of the study.

9.11 To what extent healthcare improvements should be sustained after the research is completed, and by whom, are difficult issues for researchers and sponsors. The CIOMS Guidelines (1993) (Guideline 15) states that consideration be given to the maintenance of health services and facilities in the host country once the research is over (Table 9.1). Sponsors are rarely in a position to make open-ended commitments beyond the duration of the study, particularly with regard to the maintenance of facilities or the provision of medicines. However, as a minimum, at the outset of the research, thought should be given to the impact which any temporary improvement in the quality of healthcare might have and whether this can be maintained once the study is over.

9.12 One real contribution which researchers and sponsors may be able to make is to increase the number of people able to contribute to healthcare and to assist the development and enhancement of their skills and expertise so that there is some potential for a sustained improvement in healthcare services after the study is completed. **We endorse the CIOMS Guidelines (1993) (Guideline 15) and recommend that sponsors of research should require that the development of local expertise in healthcare is an integral component of research proposals. Consideration should be given to the extent to which any strengthening of local healthcare facilities can be done in such a way that the changes are sustainable in the local context once the research is over.**

Adverse effects

9.13 On occasions, a participant in a study may suffer an adverse effect as a consequence of an intervention under evaluation. Clearly, during the study the researchers have a responsibility to care for those who may suffer such adverse effects arising from the research. But, in our view this responsibility extends also to those who suffer such adverse effects after the trial is formally ended, and to those who suffer the chronic consequences of adverse effects experienced during the study. If the adverse effect is serious, it may be detected during the course of the study, in which case the research may be halted earlier than originally intended, either by the researchers themselves or after advice from the Data and Safety Monitoring Committee (DSMC). In the case of studies of a particular treatment, it may be relatively straightforward to resume treating such participants with the previous form of treatment.

Compensation

9.14 The question of compensation for those injured or placed at increased risk of harm in the future as a result of research needs to be addressed. This issue was raised recently during the course of

a trial of a vaccine for malaria involving Gambian infants. Analysis of data from surveillance of participants from a pilot trial obtained after the main trial had started, suggested that vaccinated children were *more* at risk of malaria than children in the control group.[5] In this case, the UK Medical Research Council (MRC) provided further funds so that surveillance of participants in the trial could be intensified and facilities for the treatment of malaria in the area of the study improved. In addition, surveillance was continued for two years after the trial had been completed. Fortunately, although recipients of the vaccine were not protected from malaria by the vaccine, they were not found, on prolonged surveillance, to be at any enhanced risk of infection. No question of compensation thereby arose. Less favourable outcomes, which might raise the need for compensation, might only be revealed by routine monitoring of the participants once the trial is over.

9.15 It is also possible that a vaccine, a treatment or another form of intervention may be beneficial in the short term, but later have harmful side-effects. In addition, short-term side-effects may recur later. An example is the possibility that exposure to antiretroviral therapy in fetal or early life to prevent the transmission of HIV from mother to child may be associated with adverse effects in later life. This particular possibility is currently being addressed in developed countries through national and international collaborative studies, since the risk of adverse events may be small and would not necessarily be detected in a single study. If the therapy is widely used, even a small risk can pose a significant problem.

9.16 Researchers and their sponsors have an ethical obligation to do everything possible to minimise any harm to participants in research. If a participant in research is harmed during the course of the research, what ethical duties arise? In particular, who has responsibility for meeting any financial needs which the participant may have, for example, to pay for medical care or lost employment?[6] In general, responsibility for the healthcare of the participants is shared between the researchers and the local health authorities. But, if unexpected consequences do arise during the research, it is not always clear how the financial burden should be apportioned. Much of the national and international guidance addresses issues of compensation explicitly. For example, the Indian guidance stipulates that research proposals must include a mechanism for financial compensation to cover all foreseeable and unforeseeable risks (see Appendix 1 Table 3). In our view, issues about levels of compensation and who has the responsibility to provide it must be carefully considered and resolved between all those involved in the research before it begins.

Long-term surveillance

9.17 It is unusual for a research project in a developing country to include any long-term surveillance of those participating in research after a research study has been completed. Clearly interventions may have long-term as well as short-term consequences. In some circumstances the long-term consequences may be deleterious, even though the short-term consequences are beneficial. In trials in Guinea Bissau and Senegal, high-titre (high potency) measles vaccines, when given at a younger age than normal, induced a better antibody response at that age than conventional measles vaccines. On the basis of these trials, more widespread early use of high-titre vaccines was recommended in situations in which there were high rates of infection with measles occurring earlier in childhood than the normal age at which children would be vaccinated. However,

5 Leach A, Drakeley CJ, D'Alessandro U, Fegan GW, Bennett S, Ballou WR *et al* (1995) A pilot safety and immunogenicity study of the malaria vaccine SPf66 in Gambian infants, **Parasite Immunology**, 17: 441–4; Bojang KA, Obaro SK, Leach A, D'Alessandro U, Bennett S, Metzger W *et al* (1997) Follow-up of Gambian children recruited to a pilot safety and immunogenicity study of the malaria vaccine SPf66, **Parasite Immunology**, 19: 579–81.

6 UK public sector research funding bodies such as the MRC may not, as a matter of principle established by government, offer advance indemnities nor take out commercial insurance for non-negligent harm. The MRC only offers the assurance that it will give sympathetic consideration to claims in respect of non-negligent harm arising from an MRC-funded trial.

long-term surveillance of those participating in the studies showed that girls who received the high-titre vaccines had an increased rate of mortality several years after the vaccination, from causes not obviously related to measles. This unexpected adverse effect caused the high-titre dose vaccines to be withdrawn from general use.[7]

9.18 Risk of severe infection following early preventive measures is a particular concern in the case of malaria. Ordinarily, natural and lasting immunity to malaria follows repeated exposure to the disease for those who survive such exposures. Early preventive measures, by inhibiting repeated exposure, may enhance rates of morbidity and mortality and the likelihood of severe infection in later childhood. Several large field trials have shown that bed-nets and curtains treated with insecticide reduce overall mortality in young African children by 20–30%. There is a theoretical possibility, however, that, as a consequence of this early protection, such children may be at increased risk of contracting severe malaria in later childhood. It is still unclear whether this is in fact the case.

9.19 The two examples cited raise the question whether investigators have an ethical obligation to undertake long-term surveillance of the populations in the study. The planned surveillance of a trial population should be so designed as to enable researchers to observe both early and late effects of the intervention being tested. Ideally, all those in a trial would be followed for an indefinite period in order to detect any long-term effects of the intervention being studied. This is rarely possible even in developed countries.[8] In practically all developing countries and many developed countries, such long-term surveillance has to be specifically designed and operated and is not possible within the routine system of healthcare.

9.20 However, a paradoxical situation may arise. If an intervention is shown to be efficacious in the short term, it may be considered unethical to continue to maintain a control group, after such efficacy has been demonstrated (see paragraph 9.27). However, when the intervention is offered to those in the control group once a trial is completed, the opportunities for longer-term observation and for the detection of later deleterious effects are lost because there is no longer a control group for comparison with the participants who received the intervention. We conclude, therefore, that the course of action adopted in any particular study will depend upon the particular circumstances: the likelihood of long-term adverse effects will have to be weighed against the likely short-term benefits. This judgement, which is not confined to clinical trials in developing countries, will have to be made on a case by case basis. It will often be difficult to make and the correct balance is often only apparent with hindsight.

Provision of an intervention once the study is over

9.21 A question that researchers, sponsors and research ethics committees have to consider in research related to healthcare concerns the availability of an intervention shown to be successful to the participants in the research once the research is over. Because resources for healthcare are scarce in developing countries, this issue is often particularly difficult to address. We have seen that, for many poor people, participation in a trial may offer access to significantly better medical care and treatment (paragraphs 6.29–30). The cessation of such care and treatment, once a trial is over, has been widely criticised as exploitation of vulnerable people who generally have very limited access to healthcare and who will seldom be in a position to negotiate the extended provision of better medical care and treatment at the termination of a clinical trial.[9]

7 Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, Simondon F *et al* (1996) Child mortality following standard, medium or high titre measles immunization in West Africa, **International Journal of Epidemiology**, 25: 665–73.

8 The linkage of mortality and morbidity data with research studies over the long term poses substantial problems and is rarely feasible, except in specific cases, such as the link between mortality and cancer registries in the UK.

9 See, for example Glantz LH, Annas GJ, Grodin MA and Mariner WK (1998) Research in developing countries: taking 'benefit' seriously, **Hastings Center Report**, November–December: 38–42.

9.22 An even more difficult issue, however, is the extent of the obligation to make an intervention found to be efficacious in trials available to the wider community. Is there an ethical responsibility to ensure that an effective treatment or procedure is provided to the wider community after research is over and on whom does such a responsibility fall? In some circumstances, researchers may be in a position to take on a continuing obligation to the community in which the study was undertaken such as providing preferential access to a treatment that was developed with the co-operation of the community. It is usually difficult, however, to secure open-ended commitments to supply, for example, a new vaccine, beyond that to be used in the trial.

9.23 In the following sections, we consider what ought to be provided, and whose responsibility any such provision should be, to three groups of people: members of the control group in a trial, all of the participants in the research, and the wider community in which the trial took place. We first address the issue of the control group because this raises discrete questions that apply to research related to healthcare wherever it is conducted. We then go on to consider the provision of interventions to all of the participants in research and then to the wider community.

Providing interventions to the members of control groups

9.24 If the new intervention is shown in the trial to offer a benefit, is there an ethical obligation to offer it to the control group once the trial is complete, if they are still in a position to benefit from it? We consider that there is indeed such an obligation. In fact, such an undertaking is often given by researchers at the start of a study and may serve to persuade people to take part in the research. The nature and degree of the commitment would depend on the details of the particular study. For example, where a new medicine is being tested, treatment of the control group may be indicated when the new medicine has been demonstrated to be better than the previous one. If the new treatment is judged to be inferior, then, on the same principle, it may be appropriate to offer to treat those who received the new treatment with the standard treatment. In all cases, it should be made clear, as part of the process of obtaining consent, what is to be offered to those in the control group at the completion of the trial, and the circumstances in which it will be offered, before participants are asked to agree to take part.

9.25 The principle that those in the control group should be given the opportunity to benefit from an intervention found to be efficacious in a trial, is widely accepted in international guidance on controlled trials (see paragraph 5.13). Ordinarily, this is relatively straightforward for the researchers to arrange. For example, in trials of bed-nets impregnated with insecticide against malaria, those in control groups were given such nets once it had been demonstrated that the provision of nets reduced child mortality.

9.26 However, exceptions might arise for example if, by the end of the trial, some or all of those in the control group are not at an age, or stage of disease, to benefit from a particular treatment. In addition, it may sometimes be logistically difficult to make the intervention available to all the members of a control group. This was the case, for example, in a trial of a vaccine against infection with *Haemophilus influenzae* in The Gambia.[10,11] It was argued that not only would it have been difficult to locate and vaccinate those in the control group, who were entered into the trial shortly after birth, but also that, by the end of the trial, they had passed through the ages of greatest risk of infection and thus vaccination would confer very limited benefit.

9.27 Vaccine trials also present a further difficulty. Because most vaccines induce an immunity that declines with time, there are strong scientific grounds, when a vaccine has shown to be effective,

10 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.
11 *Haemophilus influenzae* causes a range of diseases including pneumonia and bacterial meningitis.

for maintaining the control group so that the duration of protection induced by the vaccine can be determined. However, when the control group remains at significant risk if not vaccinated with a vaccine shown to be efficacious in the short term, such an approach would be unethical. We propose, therefore, that those in control groups should be offered vaccination with the effective new vaccine on completion of the trial, if they are still at significant risk of the disease against which the vaccine is directed. As we have said, we consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24). **We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent.**

Providing interventions to all the participants in a research project once the study is over

9.28 Participants in research may have conditions that require ongoing treatment. In such cases, after a trial has ended, is there an obligation to continue to provide an intervention that has been shown to be effective to all the participants? Whose responsibility ought such provision to be? The revised Helsinki Declaration (2000) states that at the end of a study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified in the study. Extensive criticism has been levelled at this statement. While it is commendably aspirational in concept, guaranteeing the provision of an intervention which has been demonstrated to be successful may not be possible, especially in relation to ongoing treatment for chronic disease.

9.29 The NBAC Report[12] makes more specific recommendations about the provision for participants of treatment which has proved to be successful (Appendix 1 Table 5). It states that researchers, before the initiation of the trial, should endeavour to secure access for all participants to effective treatment after the trial and that the lack of any such arrangements should have to be justified to a research ethics committee.[13] The Report also recommends that research proposals should include an explanation of how any new treatment which proves to be successful will become available to some or all of the host country's population. It goes on to require that researchers must justify to the relevant research ethics committee why the research should be carried out, if this is not thought possible.[14] The National Guidelines for Health Research in Uganda go further. They state that the researcher must make every effort to ensure that a beneficial intervention is made available to the participants, as well as making all reasonable effort to secure its availability to the local community.[15]

9.30 The decision whether to make treatment available to participants in a clinical trial after the trial has been concluded will depend first and foremost on the outcome of the research. In practice, it may also be influenced by the cost of providing the intervention and supervising its administration. If prolonged treatment is involved, possibly for the rest of a participant's life (such as antiretroviral therapy for patients infected with HIV, or anti-hypertensive medicines for those with hypertension, which affects 50–10% of West African adults), it may be beyond the resources of the local health services.

12 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Maryland, USA.
13 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.
14 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.
15 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda.**

9.31 On examination, it might be shown that, if a pharmaceutical company were to provide the medicines required for the research, and the treatment were shown to be successful, this would be commercially advantageous, such that the costs of continuing to provide the treatment to participants in the trial could be offset. We repeat that it is very important that these issues be considered at the planning stage of any research, rather than debated or negotiated during the study or at its end. **We therefore endorse the NBAC recommendation that researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.**[16]

Providing interventions to the wider community and beyond

9.32 Can it be ethical to conduct research when there is little chance of making treatment shown to be successful available to the wider community? Researchers and sponsors of research have looked to international and national guidance to help them to resolve this issue. However, as we have noted, international guidance is principally in a general form and frequently difficult to apply in practice. There are, moreover, many social, political and economic factors which will influence the likely availability of a treatment shown to be successful and not all of these can be anticipated.

9.33 Several questions arise from consideration of the guidance on the availability of an intervention shown to be successful after the completion of the research, with respect to the range and scope of the responsibilities, and on whom such responsibilities fall:

- Should provision of an intervention shown to be successful be limited to the participants in research, or extended to others in the same community? If the latter, by whom?
- What is the degree of efficacy that an intervention must demonstrate, in order to warrant extensive distribution and who should provide it?
- Should all with a perceived need in the country receive the intervention and if so, for how long and who should provide it?
- Should the intervention be provided to other (neighbouring) countries which could benefit from it and who should provide it?

These questions will become increasingly pressing as more interventions, which have the potential to benefit large numbers of people are tested in developing countries. It is clearly difficult to formulate general guidance which satisfactorily addresses the wide range of different forms of intervention.

9.34 A fundamental problem that must be acknowledged is that current guidance fails to reflect the reality that only rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care.[17] For example, before mefloquine was registered as an antimalarial medicine, the WHO Special Programme for Research and Training in Tropical Disease (TDR) conducted 18 studies on three continents. Secondly, even when clinical trials have established the safety and efficacy of an intervention, there is likely to be a need for additional research studies to define the place of the new intervention in the healthcare system. Further, those participating in the trial may not be representative of the wider population, or the intervention may not be equally efficacious in another setting. For this reason, the trial may need to be repeated elsewhere and in a different setting. Research may also be necessary to determine

16 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.
17 This point also has a bearing on the question of whether it will be appropriate to continue to provide a successful treatment to the research participants once the research is over (see paragraphs 7.24–7.27)

the most effective and feasible means of making the intervention available and of achieving high uptake and acceptance by the local population. In addition, while clinical trials may show that, for example, a new antimalarial medicine is highly efficacious, policy-makers may decide to hold it in reserve while current treatments are still proving effective in order to delay resistance to the new treatment developing.

9.35 The cost effectiveness of any new intervention will also affect any decision as to its availability on a wide scale. One example of the need for cost-benefit analysis is provided by the early trials to assess the efficacy of antiretroviral treatment in reducing the transmission of perinatal HIV. The trials were performed in settings where appropriate counselling and facilities for HIV testing in pregnant women could be ensured, and where the infrastructure was such that the women were seen in hospital prior to delivery and the babies were delivered in the hospital with appropriate support and care.[18] However, this setting is not typical for women in many developing countries. A significant proportion live in rural communities with no access to counselling and testing facilities, and many undergo home deliveries. Nevertheless, following trials demonstrating the efficacy of the treatment, programmes to make the treatment available more widely were set up. These programmes were funded by a large number of national and international agencies, and assessed the feasibility and obstacles that needed to be overcome before the intervention could be extended into the wider community and nationally.

9.36 A further difficulty is that the responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.

The role of researchers

9.37 There is general agreement that researchers have some responsibility regarding the provision of an effective intervention after a trial has ended, but disagreement about how far that responsibility extends. Certainly, the main function of the researchers is to undertake research. They cannot be expected to adopt a leading role in making effective interventions available. Nevertheless, most people would agree that the researcher should present findings in such a way that healthcare policy-makers can understand their implications and, at the least, the findings can be used for advocacy purposes with respect to the future provision of the intervention.

9.38 Fundamentally, it is policy-makers who have the prime responsibility to implement changes in healthcare and to seek evidence to inform their decisions. For example, as early as the 1950s, clinical research demonstrated that the administration of at least two doses of tetanus toxoid to pregnant women could prevent neonatal tetanus. Although most health authorities in developing countries have adopted this practice, WHO estimated that there were still 270,000 cases of neonatal tetanus in 1998.

9.39 While researchers are generally not in a position to translate their research findings into action when an intervention proves to be efficacious, they can draw attention to problems which have been neglected, or conditions whose impact has been underestimated, and demonstrate that there are feasible solutions. For example, a package of simple affordable measures which reduced child mortality was identified in Nigeria in the 1960s, some of which were quickly adopted by a number of developing countries. These measures later formed the basis of UNICEF's global strategy for its programme in child survival based on GOBI-FFF (growth monitoring, oral

18 Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL *et al* (1999) Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial, **Lancet**, 353(9155) 773–80.

rehydration, breastfeeding, immunization, food supplementation, family planning, and female education). The researchers could not ensure that the Nigerian health authorities would adopt the methods demonstrated by their studies. In fact, Nigeria has been very slow in implementing the programme as originally designed or as modified by UNICEF.[19] Despite this, the research was very valuable in its advocacy of improved care for children. The iodination of salt to combat goitre in Nigeria (see Box 9.1) provides a further example of, on the one hand, the important role as advocates of better healthcare which researchers can play, while on the other hand, illustrating the limited influence that researchers may have in bringing about the prompt provision of effective interventions.

BOX 9.1 Iodination of salt

In 1975 a group of scientists led by the Chairman of the Nigeria Medical Research Council presented research data to the Nigerian Department of Health which revealed the high prevalence of goitre in the country. Attention was drawn to the impact of iodine deficiency not only in causing goitre but also in reducing the intellectual capacity of children born to iodine-deficient mothers. The group urged the government to introduce iodination into the two salt factories in which the government had investments. UNICEF had offered to cover the cost of modifying the equipment to accommodate the iodination process. It took a further 15 years of lobbying before the Ministry of Health took action.[1]

1 Lucas A (2001) Personal communication, Harvard University.

9.40 A further important role of researchers is to inform local health authorities and participants about the results of their research at the end of a study. This should be accompanied by an explanation of the implications of the results for future healthcare, or prevention of disease in the community. How such information is provided will vary in different circumstances, but as well as a written report and a verbal presentation, researchers have an obligation to answer any questions that participants or other members of the community may have about the nature and significance of their findings. The appropriate forum for this is often a public meeting. It should be noted that failure on the part of researchers to present the results of a trial is a frequent reason for participants' unwillingness to participate in any subsequent research.

The role of sponsors, international agencies, governments and other bodies

9.41 If sponsors of research were required to fund the future provision of interventions shown to be effective to research participants or the wider community, many would cease to support such research. Sponsors from the public sector, such as the UK MRC or US NIH, would simply be unable to bear the costs involved without curtailing other research. Although the financial resources of many pharmaceutical companies are large, many of them would be equally reluctant to take on the additional burden of long-term commitment.

9.42 Any intervention shown to be effective in a research study may not be generally adopted because of cost. Although a successful national trial of bed-nets treated with insecticide in The Gambia reduced overall child mortality from malaria by approximately 30%, it was decided by the researchers, sponsors and the Gambian Ministry of Health that when the research was implemented nationally the cost of the insecticide would have to be recovered because the Ministry could not afford to provide free insecticide indefinitely. Charging for insecticide led to a reduction in the number of young children sleeping under an insecticide-treated net from around 70% to 20%.[20]

19 Lucas A (2001) Personal communication, Harvard University.
20 Cham K, Olaleye B, D'Alessandro U, Aikins M, Cham B, Main N *et al* (1997) The impact of charging for insecticide on the Gambian national impregnated bednet programme, **Health Policy and Planning**, 12: 240–7.

9.43 It should be borne in mind that while interventions may initially be too costly to be made available, costs may subsequently fall. This was the case with the hepatitis B vaccine used in The Gambia (see Box 1.3). On occasions, manufacturers of vaccines or sponsors of research might agree to supply substantial quantities of a vaccine free or at subsidised cost after the successful completion of a trial. This was done, for example, following trials of *Haemophilus influenzae* (Hib) vaccine in The Gambia, but it was not possible to secure an initial commitment beyond five years.[21] The issue of how large a population might be included in such a scheme also arises. The Gambia is a small country (about one million inhabitants), and commitments extending to much or all of the country have been secured following trials there. Such a commitment may be much more difficult to secure in a larger country, for example Nigeria or India, such that it might have to be limited to a region, or part of a region. The pharmaceutical industry is involved in various donation programmes and partnerships (see paragraph 2.35). An example is the ongoing donation of Ivermectin. This treatment, originally developed for treating animals for worm infestation, was found to be highly effective against onchocerciasis (river blindness) in humans, but was too expensive for use in developing countries. However, the pharmaceutical company that produced the medicine decided to provide it at no cost for the treatment of onchocerciasis and WHO has managed the distribution to countries in onchocerciasis-endemic areas.

9.44 In some circumstances, the results of a successful study may influence national policy and bring pressure to bear on providers of health services to make the intervention available. In a recent study in Uganda, oral nevirapine was administered to pregnant women infected with HIV at the onset of labour, and the newborn babies received nevirapine syrup within 48–72 hours after delivery. The study showed a 50% reduction in transmission of HIV-infection from the mother to the baby at 14–16 weeks in the group receiving nevirapine, compared to the control group which received AZT alone. The Ugandan government acted on the findings of the study and introduced a policy of providing the treatment involving nevirapine to all pregnant women who were HIV positive. The cost of treatment is relatively low, about US $4 per person, but this is still more than most countries in which HIV is endemic can afford. The pharmaceutical company concerned has recently announced that it will offer the medicine free of charge for use in the prevention of transmission of HIV from mother to child in developing countries.[22] That said, the programmes of treatment do not depend merely on the cost of the medicines. It is the voluntary counselling and testing, an integral part of these programmes, as well as the need for an appropriate infrastructure for the delivery of healthcare that account for the greatest cost. Finally, quite apart from considerations of cost it is important also to bear in mind the broader benefits for women and infants that may arise from a more widespread improvement in antenatal care. These examples have led us to conclude that the fact that a particular intervention is currently expensive should not necessarily rule out the possibility of its being evaluated in a developing country.

9.45 As we have seen, the costs of some interventions shown to be successful may not decline significantly until some time after the conclusion of the research. To describe all such research as therefore unethical may lead to the loss of opportunities to improve healthcare. At the same time, several factors would need to be taken into account before the testing of costly medicines could be justified, including the extent of the prevalence of the condition being studied in those participating in the research, whether the disease is acute or chronic, and the complexity of and feasibility of delivering the regime of treatment. In particular a research ethics committee would need to be persuaded of the need to carry out the study in a particular community. Whether or not provision for ongoing

21 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.
22 Boehringer Ingelheim has offered to supply VIRAMUNE® (Nevirapine) free of charge for the prevention of mother-to-child transmission in developing economies. Supplies of medicines have already been made to the Republic of Congo and to Senegal.

treatment beyond the end of the trial are in place should also be clearly explained to prospective participants before their consent is sought.

9.46 While the prime responsibility for continuing healthcare in a community lies with the local health authorities, we take the view that researchers also have some responsibility for what follows from the research which they conduct. A close dialogue should be maintained with the local authorities before a trial begins and at all stages of the trial. For an intervention which has a low cost, the issue of its continued availability to participants may not arise, except for concerns as to whether there is the necessary infrastructure to deliver the intervention, although in poor communities this is often a very significant consideration. For interventions which have a high cost, as we have seen, continued availability may be much more problematic.

9.47 Of particular concern has been the suggestion that some clinical trials in developing countries have been conducted not for the benefit of those in developing countries but largely for the benefit of those in developed countries. A possible example may be the evaluation of low cost schedules of HIV treatment (see Box 1.2). While finding less expensive, but effective, treatments for infection with HIV is a high priority for developing countries, it would also be of significant interest to developed countries. It should be recalled that the price of cheaper treatments may still be beyond the resources of most developing countries.

9.48 **In light of the issues discussed above, we recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:**

- **the need where appropriate to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research**
- **the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time**
- **the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful.[23]**

9.49 **We endorse the NBAC recommendation that research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committee why the research should be carried out if this is not thought possible.[24]**

The development of expertise in research

9.50 In 1990, the Commission on Health Research for Development identified the strengthening of expertise in research as 'one of the most powerful, cost effective and sustainable means of advancing health and development'.[25] During the decade which followed, efforts were made to strengthen expertise in research by national and international organisations. However, these

23 This consideration is especially important for expensive interventions.
24 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.
25 Cited in Health Research for Development: the continuing challenge, a discussion paper prepared for the **International Conference on Health Research for Development**, 10–13 October 2000, Bangkok.

efforts have been criticised for being fragmentary and not sufficiently endorsed and advanced by individual countries.[26] Indeed, very few developing countries have a systematic plan for developing such expertise. Despite the great need for research to identify the most effective healthcare interventions for developing countries, the extent of expertise to undertake this task at a local level is severely limited. This is due largely to insufficiently trained personnel and a lack of a critical mass of researchers. The few who are well trained and able are often in great demand and may be recruited by multinational companies or international health agencies, further reducing the expertise available for areas of national priority.[27] It is very important, therefore, that research in developing countries, particularly when sponsored by developed countries, is used as a platform for enhancing the skills of scientists in those developing countries. The concept of 'safari research', in which the researcher from a developed country visits a developing country merely to collect samples or data to be studied elsewhere, is ethically unacceptable.

9.51 Genuine partnerships should be promoted in order to strengthen expertise in research and institutional development and to maximise opportunities for the transfer of skills and knowledge. Genuinely collaborative research projects generate opportunities for training and for developing human resources. Such collaborations can increase self-reliance in developing countries, thereby enabling local specialists to identify areas needing research and to develop local solutions to public health problems. The development of operational guidelines for healthcare, systems for surveillance and management flow-charts are potential by-products which in turn contribute to the improvement of healthcare systems and the ability of countries to respond to their public health needs.

9.52 Once research is completed, there are occasions on which complicated and expensive research equipment may be left behind, or donated by the researchers from the developed country. If local scientists and technicians have not received sufficient training to maintain and use the equipment effectively, or if resources for maintenance of equipment are not available, the opportunity for improving the ability to conduct research locally will be lost. Funds for the maintenance of equipment and development of appropriate training programmes need to be included in the costs of the original research project. Equally, the costs of facilitating training, so as to ensure that equipment can be used and is maintained beyond the particular research project, should be considered. We note that guidance such as that of the Medical Research Council of South Africa (2002)[28] explicitly emphasises the need for the development of research expertise to be addressed before research is conducted. **We recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries. Consideration should also be given to the development and support of expertise so that equipment obtained for the purposes of a research project can continue to be used and maintained.**

26 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.

27 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.

28 Medical Research Council of South Africa (2002) **Guidelines on Ethics for Medical Research: General Principles**, Medical Research Council of South Africa, Tygerberg: Paragraph 11.4.4i.

Section 4

Conclusions and recommendations

Chapter 10

Conclusions and recommendations

Introduction

10.1 Many people in developing countries suffer from poor health and reduced life expectancy. Poverty, coupled with limited scientific, administrative and political development often makes it very difficult for developing countries to improve healthcare. Those who seek to improve the health status of developing countries do so against this background, in which poor health is a reflection of the larger inequality. We have focused on one aspect of healthcare, that of research. Developing countries urgently need research related to healthcare which addresses their burden of disease. It is therefore axiomatic that externally-sponsored research that seeks to bring health benefits, should, with appropriate safeguards, be encouraged in developing countries. We consider, moreover, that there is virtue in research which provides not only direct benefits to participants such as treatments for specific health needs but also indirect benefits arising from the influx of resources into a local community and the enhancement of expertise in research.

10.2 We ask how the conduct of healthcare research in developing countries, much of which is funded by sponsors in developed countries, can be consistent with principles of justice. Our primary focus is not on the existence of injustice on a global scale but on its implications for those who have the power to act, whether within or outside of developing countries, including governments, research councils, private companies and researchers. The inequalities in resources between external sponsors of research into healthcare, and communities and governmental authorities in the developing countries, will often be so great that there is a real risk of exploitation in the context of externally-sponsored research. It is crucial therefore that the four principles which form the ethical framework for this Report: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences and the duty not to exploit the vulnerable are respected when research is planned and that appropriate safeguards are put in place.

10.3 The Working Party has made a number of recommendations to guide external sponsors of research related to healthcare. While these recommendations are, for the most part, directed to external sponsors, this is not to suggest that the principles on which they are based are not equally applicable to internally funded, national research. The recommendations, taken together, should be regarded as a framework for the ethical conduct of research, whoever the sponsor might be.

10.4 Our central aim has been to consider how individuals and organisations from developed countries should conduct themselves when sponsoring or undertaking research related to healthcare in developing countries. We have examined the ethical issues raised by externally-sponsored research and considered ways in which they might be resolved. The disparity between the resources and power of the external sponsor of research and the developing country has been central to the discussion. We recognise that external sponsors, whether they be multinational pharmaceutical companies or publicly funded research organisations, may differ in their motives for undertaking research related to healthcare in developing countries. Despite these differences, we consider that all externally-sponsored research should be required to fall within the ambit of the national priorities for research related to healthcare within developing countries, unless the reason for not doing so can be justified to the appropriate research ethics committee within that country. Not only must the people who are part of that research be treated with respect, but the balance between the interests of these individuals and the interests of the wider community from which they are drawn must be carefully weighed.

10.5 When planning and conducting research, researchers and their sponsors have a duty to recognise the importance of national and local cultures and social systems, values and beliefs. In addition, external sponsors have an obligation to educate and train members of the local and national communities in the methods and skills of conducting research. The need for research projects to

be subjected to review as to their ethical propriety is paramount. There is an urgent need for further education and training to ensure that those in developing countries are able to discuss ethical issues effectively with external sponsors and others and to have mechanisms in place to deal with issues that arise. Most importantly, research ethics committees in developing countries have the responsibility of sanctioning only that research which is appropriate and of challenging and preventing research that is not.

10.6 The four main topics of our Report – standards of care, consent, the ethical review of research, and what happens when the research is over – emerged as we examined the subject in detail and in response to questions raised during our deliberations. Some of the recommendations which we make on these topics have been directed to particular agencies with a view to their taking them forward. We also set out an agenda for action by those in developing countries so as to develop expertise in the conduct of research and effective procedures for the ethical review of research proposals.

Healthcare economics

10.7 The major inequalities in health which exist across the world are closely related to levels of social and economic development. The burden of disease in the majority of developing countries is enormous. The active participation of many agencies will be required if change is to be achieved. Research on new forms of interventions and on more effective ways of delivering new or existing interventions is crucial. The cost of the process of evaluating a new intervention through clinical research can be very high; so high that it could not be covered by many developing countries without external support. In addition, many forms of interventions, especially new medicines and vaccines, may be very costly to manufacture or purchase. However, there are examples which show that, once an intervention, such as a medicine or a vaccine, has been shown to be effective, ways may be found of substantially reducing the costs of providing such an intervention to a developing country. Despite the great need for research to determine which forms of intervention in developing countries are most effective, the capacity of those countries to conduct relevant research is severely limited. Developing expertise in research to help countries to set their own priorities and to focus research on those priorities is a crucial obligation that sponsors of externally-funded research must acknowledge.

Setting priorities for research

10.8 Setting priorities for healthcare research is a particularly important issue in developing countries, because national resources for research are generally very limited. Clearly, the more a country can determine its own priorities and conduct its own research, the easier it will be to ensure that research proposed by external sponsors is appropriate and relevant to its national health needs. If there is no clear picture of the priorities for research related to healthcare within a country, it will be more difficult for government and external sponsors to collaborate in addressing them.

10.9 It follows that to enable effective collaboration with external sponsors, developing countries should have a mechanism allowing them to set priorities for research into healthcare, together with a robust mechanism for scientific review and ethical review of any proposed research (see Chapter 8). How this is managed will depend on the resources available in each country. **We therefore endorse the view of the Commission on Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991) that all countries should set priorities for research into healthcare (paragraph 2.31).**

Failure to do so may mean that external sponsors wishing to conduct research will be unable to identify a country's crucial needs as regards research into healthcare and therefore may be more likely to propose inappropriate research with little relevance to the country in which it is conducted.

10.10 We do not take the view that all externally-sponsored research should fall within nationally defined priorities, since all research has the potential to contribute to the development of local skills and expertise, quite apart from the inherent value in diversity of research. However, there is a careful balance to be drawn. The inherent inequalities of power and advantage between developed and developing countries require that particular care is needed to restrain any tendency on the part of the sponsor to pursue their interests to the detriment of those of the host country. **We therefore recommend that when research funded by external sponsors is proposed which falls outside the national priorities for research into healthcare set by a host country, those proposing the research be required to justify the choice of the research topic to the appropriate research ethics committees in both the host and sponsoring countries (paragraph 2.32).**

Social and cultural issues

10.11 Systems of biomedical care in developed countries are generally based on common scientific assumptions. There are, however, a variety of other systems of diagnosis and healing which may vary a great deal across cultures and countries. This is particularly true of developing countries. Research into healthcare conducted along scientific lines in a particular society, or culture, will be affected by existing assumptions and practices. In any research in developing countries, therefore, these need to be addressed. Particular attention will need to be given to the means of informing potential participants about the proposed study and the process of seeking their consent. The differing conceptions of what respect for persons entails in many societies in the developing world, and the need for the community to discuss issues and reach agreement as a first step in the approval of a research project must be taken into account by researchers.

10.12 Research which pays no regard to the development of local infrastructures, or which fails to make appropriate use of local systems, skills and practitioners, may fail to maximise the benefit of the research to the community. The possibility and desirability of co-operation between practitioners of traditional medicines and scientific researchers on a particular research project should be considered on a case-by-case basis.

Ethical principles

10.13 The Working Party identified four ethical duties that are crucial in evaluating the actions and policies of individuals and organisations proposing to carry out research in developing countries. The four duties are the duty to alleviate suffering, to show respect for persons, to be sensitive to cultural differences, and the duty not to exploit the vulnerable. They constitute a framework for articulating the duties, obligations, claims and expectations of those involved in research related to healthcare. The practice of medicine is intrinsically justified by virtue of the duty to alleviate suffering. Research into healthcare makes an essential contribution to the alleviation of suffering. While the needs of our own communities may generally have the first claim on our resources, we have a duty to contribute to the alleviation of suffering elsewhere. Thus, there is an ethical imperative to conduct research, including that which addresses the health problems of developing countries.

10.14 The principle of respect for persons places important constraints on the performance of the duty to alleviate suffering. That duty, by itself, may lead us to the assumption that the less

suffering there is, the better the world is overall. However, the principle of respect for persons enjoins us to consider carefully the ways in which we seek to alleviate suffering. For example, policies which violate other interests of those involved, even if they offer the most straightforward way of reducing suffering, are to be weighed carefully.

10.15 An important characteristic of externally-sponsored research conducted in developing countries is that there are often cultural differences between those organising or funding the research and the researchers and participants in the host country. One potentially potent misuse of power is to be insensitive to the cultural perspectives that individuals bring to questions of health and healthcare. Indeed, the variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. It may be claimed that the requirement to practice sensitivity to cultural differences leads to moral relativism, which is the view that different moral codes cannot be critically compared and evaluated. In our view, the existence of cultural diversity does not lead to moral relativism. Sensitivity to the values inherent in local practices does not require uncritical acceptance of them. What is required is a willingness to explore differences without prejudice and to seek as far as possible to understand them, informed by knowledge of local traditions and material circumstances.

10.16 We suggest that, as a matter of moral principle, the more powerful have a duty to refrain from exploiting to their own advantage the vulnerability of the weaker. Just as it is unacceptable that local political and economic elites should seek to pursue their own goals at the expense of populations participating in research, so it is unacceptable that researchers should select populations which are economically or politically weak and therefore vulnerable to exploitation, in order to test therapies more cheaply or in order to use the results for the benefit of other, more wealthy, communities.

The framework of guidance

10.17 The Working Party noted that an ethical inquiry does not concern itself only with the articulation of appropriate general values and principles; it has also to concern itself with the institutions and procedures through which these principles are put into practice. Researchers and sponsors who undertake research related to healthcare in developing countries are faced with difficult choices. On the one hand, they need to be sensitive to the local social and cultural context, while on the other they need to ensure that their clinical methods reflect the obligations imposed by the relevant national and international guidance. In practice, researchers and sponsors have been confronted with guidance which is often generalised and even contradictory. Nor has the guidance generally taken into account the special circumstances which characterise externally-sponsored research in developing countries.

10.18 The Working Party has concluded that training in interpreting and applying the guidance is an important accompaniment to the guidance itself. Unless guidance is clearly understood by researchers, sponsors and the members of the research ethics committees, it will be of little real value. So that a common understanding is established between researchers in both developing and developed countries, we suggest that education and training of those involved in biomedical research is undertaken so that the requirements of the guidance are clearly understood and implemented. **We conclude that in any revised or new guidance the provision of training in the ethical conduct of research should be a requirement placed on all involved in the sponsorship of research in developing countries (paragraph 5.26). We recommend that national and international sponsors of research, including government agencies and departments, charitable foundations and pharmaceutical companies, ensure that provision is made for education and training in the ethics**

of research of all of those professionals involved in research related to healthcare to ensure that the requirements of relevant guidance on ethics are met (paragraph 5.27). In addition, we encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application (paragraph 5.28).

Consent

10.19 The fundamental ethical duty of respect for persons requires that we do not act against a person's wishes, and thus genuine consent to participate in research must be obtained. For consent to be genuine, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made. It must include such matters as the nature and purpose of the research, the procedures involved and the potential risks and benefits.

10.20 An awareness of the social and cultural context in which research is to be conducted is required, so that communities and individuals can be informed of any aspect of the research that may cause them particular concern. The process of obtaining consent also needs to be designed to provide opportunities for participants to ask questions of personal interest about the proposed research.

10.21 In some circumstances there is a tension between the requirement that genuine consent to research be obtained, and cultural contexts in which giving certain information, such as a diagnosis of a serious disease to a patient, is not customary. The Working Party has considered these competing interests and has concluded that obtaining genuine consent to research from participants is vital in ensuring that respect for persons is promoted. Without appropriate information, participants in research may be harmed by being exposed to risks or dangers that they would prefer to avoid. In addition, they will be denied the opportunity to learn more about their condition, possible treatments, and any beneficial outcomes of the research. Consequently, when research is conducted in contexts in which information about diagnoses and options for treatment is not normally provided, care and sensitivity will be required to design appropriate consent procedures, so that participants receive appropriate information about research and genuine consent may be given.

10.22 For consent to be genuine, it must be freely given. In some societies it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders. Three such situations can be distinguished: consultation is required with the community before individuals are approached about research; permission from a leader(s) of the community is required before any research is discussed with the community or individuals; the leader of the community is considered to have the authority to enrol participants in research. In each of these circumstances, to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm relationships within that community and between a community and researchers. We noted in Chapter 4 that we cannot avoid the responsibility of taking a view when the two aspects of respect – respect for culture and respect for persons – come into conflict with one another. We are of the view that the fundamental principle of respect for persons requires that participants who have the capacity to consent to research should never be subjected to research without such consent. The Working Party has concluded that assent from others may be necessary before research is conducted, but that it is not sufficient: individual participants must receive appropriate information about the research and be asked to give consent. To ensure that individual participants can make up their

own minds without undue communal pressure, anonymity for those who wish to decline to participate in research should be assured. **We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected. Researchers must not enrol such individuals and have a duty to facilitate their non-participation (paragraph 6.22).**

10.23 Participants in research may have a variety of motivations for taking part in research. The healthcare that a participant would receive as part of a research programme may amount to a significant inducement to take part. Researchers will need to be aware that when research is conducted in developing counties, prospective participants may have little or no alternative means of receiving healthcare for a condition, other than through the facilities supported by the research, and thus the healthcare provided as part of the research will amount to a significant inducement to participate. In addition, benefits unrelated to the research protocol, such as financial payments, may be offered to compensate for travel costs or time devoted to the research. The dividing line between acceptable and inappropriate inducements is a fine one. The larger an inducement, the more likely it is to be inappropriate, because it causes an individual to expose himself or herself to risks or potential harms that he or she would otherwise consider to be unacceptable. In addition, payments and other benefits unrelated to the research protocol will act as significantly greater inducements in developing countries than would similar amounts in more developed contexts. **We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees (paragraph 6.32).**

10.24 Concerns have been expressed that consent forms and information sheets used for research in developing countries may contain terms that are commonly used in the countries of those sponsoring the research but are inappropriate in the context in which the research is being conducted. Various forms of guidance give detailed indications of the matters about which participants should be informed.[1] It should always be remembered that such devices as information sheets and consent forms are intended to assist the consent process. Researchers will need to refer to the relevant guidance and consider which matters are relevant to their research and to the context in which the research is to be conducted, and how to express the information they seek to convey. Forms which are long, complex and inappropriate for the cultural context in which they are being used, are likely to confuse, rather than inform, participants in research, and should not be approved by research ethics committees.

10.25 There are circumstances in which, while genuine consent to research can be obtained, it may be inappropriate to ask participants in research to sign consent forms, no matter how well designed. One obvious example is when research is being conducted in an illiterate population. The Working Party considers that it is not consistent with the duty of respect for persons to require a prospective participant to 'sign' a written consent form that they are unable to read.

1 For example, Guideline 2 of the CIOMS 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects specifies 10 pieces of essential information which should be given to prospective research participants, including: the aims and methods of the research, the benefits that might reasonably be expected to result to the research participant or to others as an outcome of the research, any foreseeable risks or discomforts, the extent of the investigator's responsibility, if any, to provide medical services to the research participant, confidentiality of participant data and arrangements for compensation for research-related injuries.

In such circumstances other means of recording genuine consent to participate is required, to protect participants from being enrolled in research that they have not consented to. **Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given. Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent (paragraph 6.40).**

Standards of care

10.26 There has been significant international debate about the standards of care that should be provided to participants during externally-sponsored research in developing countries. In this Report, we have focused on the question of whether participants in the control group of a research trial should be provided with a universal standard of care, regardless of where the research is conducted. The different approaches that have been proposed when deciding the level of care that should be provided for those in the control group of a clinical trial can be divided into two broad categories:

- universal: the best treatment available anywhere in the world, wherever the research is conducted
- non-universal: the treatment available in a defined region.

10.27 The Working Party is firmly of the view that the need to avoid exploitation is imperative. It is a fundamental ethical principle that those involved in research should not take advantage of the vulnerabilities created by poverty or a lack of infrastructure and resources. However, the Working Party considers is that insisting upon a universal standard of care may not always be the best way to respect this principle.

10.28 At first sight, justice might seem to require that we treat people identically, regardless of context, because justice demands equal respect. If showing respect for the participants in a particular research project in the developed world demands that they receive a particular intervention, it would seem to follow that participants in similar research conducted in the developing world should receive the same intervention. To apply a lower standard of care would thus be not only to take advantage of the participants' vulnerabilities, but also to commit an additional wrong by perpetuating an injustice. However, the principle of equal respect does not imply that we must behave towards others in a uniform manner, since features of individuals and of their circumstances will differ. Parity of respect requires us to address the specific needs and circumstances of individuals in determining how to behave towards them. What we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a [relevant] reason should be given'.[2] Thus, equal respect for participants in research does not necessarily entail that they should receive equal treatment, regardless of where the research may be conducted. Instead, the circumstances in which the

2 See Williams B (1973) The Idea of Equality, in Williams B **Problems of the Self,** Cambridge University Press, New York, for a clear exposition of this point.

research will be conducted must be critically assessed to establish whether or not the variations in circumstances provide a morally relevant reason for offering a different standard of care.

10.29 We take the view that, in determining the appropriate standard of care to be provided to participants in the control group of a research trial, a number of factors should be considered by sponsors, researchers, and research ethics committees. These include:

- the appropriate research design(s) to answer the research question (in some situations only one research design may be appropriate to answer the research question, in others a number of research designs, in which different standards of care are offered to the control group, may be possible)
- the seriousness of the disease and the effect of proven treatments
- the existence of a universal standard of care for the disease or condition in question and the quality of the supporting evidence
- the standard(s) of care in the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can be afforded by the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can effectively be delivered in the host country(ies) during research
- the standard(s) of care which can be provided in the host country(ies) on a sustainable basis.

10.30 Taking the above considerations into account, in some circumstances, it will be clear that a control group in a clinical trial should receive a universal standard of care, wherever they live. In contrast, there are situations in which it is clear that even if there were an agreed universal standard of care for a disease, it may not be possible for this standard to be provided to the control group in a research project. This may be because of practical considerations, for example because the country in which the research is to be conducted may not have the infrastructure to provide such treatment, or because research using such a standard of care would have little relevance to the country in which it is conducted. The decision about whether or not a universal standard of care should be provided to the control group is usually not straightforward and involves careful consideration of the factors outlined above.

10.31 Where it is not appropriate to require that a universal standard of care be provided to the control group in the light of all the relevant circumstances, questions arise about what standard of care should be provided. The ultimate goal of research must be to provide information about treatment and other interventions which can then be used by national governments to ensure that improvements are made in the provision of healthcare. Thus, for policy reasons, it seems sensible to take the particular country as the unit of focus, as it is national governments which, by and large, take responsibility for the health of their citizens and which make decisions about the provision of healthcare. With knowledge of the resources available to them, governments make decisions about the level of care which they can provide for the prevention and treatment of specific diseases or conditions. In that context, they set targets for the level of care that they will strive to achieve, often recognising that it will not be possible to meet this goal.

10.32 The Working Party is of the view that in externally-sponsored research, the level of care that ought be offered to participants should, as a minimum, be the standard that the country endeavours to provide nationally. In many circumstances, it may be appropriate for researchers to offer a higher level of care than this, while still conducting research that is relevant to the local setting.

10.33 We conclude that discussion with clinicians, researchers and representatives of government and health authorities within the host country is essential so as to establish what the best national level of treatment available as part of the national public health system is. **We recommend that in setting the standard of care for the control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system (paragraph 7.29).** In research that aims to improve current forms of treatment within a developing country it may be proposed that the standard of care to be provided to the control group is lower than the best available intervention as part of the host country's public health system. In exceptional circumstances such research may be justified (see paragraphs 7.30–7.31).

10.34 In some forms of research, such as those designed to determine the incidence of a disease in a population, or to prevent participants from contracting or developing a disease, the standard of care received by participants who develop the disease will not be immediately relevant to the research. Under these circumstances, however, there is still a need to consider the standard of care which a patient should receive because the disease, once diagnosed, may have serious implications for the individual. The issue was the subject of extensive consultation when the UNAIDS guidance on ethical considerations in research on a HIV preventive vaccine was drafted. **We endorse Guidance Point 16 of the UNAIDS guidance on Ethical Considerations in HIV Preventive Vaccine Research.[3] We conclude that when research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease under study. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease (paragraph 7.33).**

10.35 During research into some diseases, participants may develop a condition that is related to the condition under study or an entirely unrelated condition. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a centre where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system. This is a complex issue and decisions will need to be made on a case-by-case basis following discussion with clinicians, researchers and representatives of government and health authorities within the host country. **We recommend that before research begins, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard must be justified to the relevant research ethics committees (paragraph 7.35).**

3 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document**: Guidance Point 16: Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial, taking into consideration the following: level of care and treatment available in the sponsor country; highest level of care available in the host country; highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country; availability of infrastructure to provide care and treatment in the context of research; and potential duration and sustainability of care and treatment for the trial participant.

Ethical review of research

10.36 The requirement that the ethics of research related to healthcare is subject to review is designed to protect participants in research. The Working Party considers that each proposal for externally-sponsored research in developing countries should receive three levels of assessment: relevance to priorities in healthcare within the country(ies); scientific validity; and ethical acceptability. While research ethics committees are not constituted to make decisions about whether or not the findings of research can be implemented within a country, they should, however, determine if the implications of possible research results have been discussed, including the possibility of ongoing provision of treatments shown to be successful. Research ethics committees must also be satisfied that appropriate scientific review of research has taken place. We accept that it is not possible to separate entirely the processes of reviewing the science and ethics of a research proposal, but as the two forms of review have quite different purposes we conclude that they should, where possible, be kept separate (paragraph 8.5). This may, but will not necessarily, require the establishment of separate committees.

10.37 We have outlined a number of issues which research ethics committees need to consider when reviewing externally-sponsored research. These include the appropriateness of procedures for giving information about the research to prospective participants and communities and recording consent; the standards of care that should be provided to participants in research and arrangements that have been made for post-trial access to interventions.

10.38 The mere presence of a research ethics committee in a country is not enough to ensure that research will be adequately reviewed. Committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience of, ethical review. An effective system for ethical review is a crucial safeguard for participants in research. **We recommend that all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees**. Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. **In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level (paragraph 8.16)**.

10.39 In developing countries, research ethics committees may have access to only limited administrative or financial support. To meet the costs of effective review, some research ethics committees receive regular funding from government. Others levy fees for reviewing research protocols. Regardless of whether the financial support for research ethics committees comes from government, research institutions or as a result of levying fees for review, it is crucial that the independence of research ethics committees be maintained. **We conclude that there is a need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research (paragraph 8.20)**.

10.40 In order to ensure that acceptable ethical standards are observed in externally-sponsored research, research should be approved through a system of ethical review of research in both the host and the sponsoring country. As regards the latter, if a sponsor provides funding, it must

have the means of ensuring that the funds are being used in a manner that is ethically acceptable. However, the country in which the research is to be conducted must also be satisfied about the ethical acceptability of the research. **We recommend that externally-sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted (paragraph 8.22)**. Should there be disagreement between committees in the developed and developing country(ies), negotiation between the committees in the sponsor's country and the country in which the research is to be conducted may be required. There should be mechanisms available to facilitate such negotiation. Where there are irreconcilable differences between research ethics committees, a committee may choose not to approve the research.

10.41 For research ethics committees to function effectively, committee members must receive adequate training. A number of national and international programmes are being established to develop expertise in ethical review in developing countries. Concerns have been expressed that training programmes for members of research ethics committees in developing countries, sponsored by a single developed country, may tend to reflect the views and procedures of the sponsoring country. **We recommend that international programmes and organisations, including the World Health Organization (WHO), continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees. Funding should be provided to these international programmes for such purposes by bodies that sponsor research in developing countries (paragraph 8.29)**.

What happens once research is over?

10.42 Once an externally-sponsored research study is completed in a developing country, the researchers and their sponsors are confronted with a number of issues relating to the future provision of healthcare benefits to the participants in the research and to the wider community. Many have taken the view that to fail to provide treatment which has been shown to be successful to the participants in research is ethically unacceptable. We take the view that in general, it is the responsibility of governments and not researchers or sponsors to determine the level of healthcare and the range of treatments and medicines that are provided to populations. However, researchers and sponsors often directly contribute to the strengthening of local healthcare facilities, so as to facilitate the research and to act as an inducement to individuals to participate. In addition, researchers may and frequently do act as advocates for the adoption of a medicine or vaccine shown to be successful. We recognise that sponsors are rarely in a position to agree to open-ended commitments once the research is completed, whether for the maintenance of facilities for healthcare or for the provision of interventions, but these are issues that need to be discussed and agreed by the research ethics committee, to the extent possible, before the research is initiated.

10.43 In externally-sponsored research, a valuable contribution can be made towards the development of local expertise during the research, so that there is the potential for continued improvement in healthcare once the research is complete. **We endorse the Council of International Organisations of Medical Sciences (CIOMS) Guidelines (1993) (Guideline 15) and recommend that sponsors of research should require that the development of local expertise in healthcare is an integral component of research proposals. Consideration should be given to the extent to which any strengthening of local healthcare facilities can be done in such a way that the changes are sustainable in the local context once the research is over (paragraph 9.12).**

10.44 With regard to the provision of an intervention shown to be successful once the research is completed, there are three groups of people to be considered: members of the control group in a trial, all of the participants in the research project, and the wider community in which the research took place.

10.45 The principle that those in the control arm of a trial should be provided with the intervention when it has been demonstrated to be efficacious is widely acknowledged. We consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24). **We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial, where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent (paragraph 9.27).**

10.46 Participants in research may have conditions that require ongoing treatment. In such cases, it may be suggested that there is an obligation to continue to provide an intervention that has been shown to be effective to all participants. While such a requirement would be commendably aspirational, it may not be possible, especially in relation to ongoing treatment for chronic diseases. **We therefore endorse the US National Bioethics Advisory Commission (NBAC) recommendation that researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee (paragraph 9.31).**[4]

10.47 The most contentious issue concerning the future provision of benefits arising from research related to healthcare is the availability of successful interventions to the wider community once research is over. The Working Party acknowledges that if sponsors were required to fund the future provision of effective interventions, the majority would no longer support such research. Provision of a successful intervention to the wider community is primarily the responsibility of governments. However, there have been significant contributions from the pharmaceutical industry, although these are, by necessity, seldom open-ended. We have concluded that the complexity of the circumstances relating to the availability of interventions after the completion of a trial makes it difficult to formulate general guidance which applies to different forms of interventions. The need for further research, the role for research relating to the local delivery of interventions, the change in the cost of medicines, the existing framework for healthcare, and the commitment of policy-makers, are all factors which will influence the availability of a successful intervention. Despite these uncertainties, we conclude that there is a duty on researchers to address the issue before any research is initiated.

10.48 **We recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:**

- **the need, where appropriate, to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research**
- **the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time**

4 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.

- **the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (paragraph 9.48).**[5]

10.49 **We endorse the NBAC recommendation that research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committee why the research should be carried out if this is not thought possible (paragraph 9.49).**[6]

10.50 Despite the very great need for healthcare research in developing countries, local expertise in research tends to be severely limited. It is therefore particularly important that sponsors of research promote genuine partnerships between researchers in developed and developing countries when research is externally sponsored in order to strengthen expertise in research and maximise the opportunity for the transfer of knowledge and skills. **We recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries. Consideration should also be given to the development and support of expertise so that equipment obtained for the purposes of a research project can continue to be used and maintained (paragraph 9.52).**

Concluding comments: a framework for future action

10.51 In this Report, we have set out an ethical framework for assessing the duties and responsibilities of those involved in designing and conducting research related to healthcare. The framework is based on four principles: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences and the duty not to exploit the vulnerable. Rather than formulating a strict prescription of conduct which these principles would require when research in developing countries is externally sponsored (such as stipulating that a universal standard of care be provided), we have emphasised the critical importance of taking social, cultural and economic contexts into account when applying these principles, and have identified the minimum requirements which must be met in all circumstances. Particular care is required in those countries which do not have well established procedures for the protection of participants in research.

10.52 We are aware that researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometimes conflicting guidance. Our contribution therefore has been to present an ethical framework as a guide for others to use when determining how to apply the guidance. In particular, the development of national guidance and the strengthening of the process of ethical review of research are priorities for developing countries which will afford a further layer of protection to participants in research.

10.53 In this Report we have argued for approaches to consent, standards of care, ethical review and the future provision of healthcare that take into account not only the need to protect participants in research, but also the economic realities that are faced by the majority of developing countries. In doing this, it is crucial that the recommendations in this Report are taken as a whole. Thus, the flexibility in tailoring standards of care and procedures for obtaining consent for specific research projects must be accompanied by the development of a rigorous and effective process of ethical review that assesses the appropriateness of the proposed research. This will allow research to be designed so that it has the greatest chance of providing relevant information about a population and thus alleviating suffering, without risking exploitation of vulnerable communities.

5 This consideration is especially important for expensive interventions.
6 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.

Appendix 1

Guidance on research related to healthcare

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI[1]

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.'

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

1 Reproduced with permission from the World Medical Association.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of

the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

NOTE OF CLARIFICATION ON PARAGRAPH 29 OF THE WMA DECLARATION OF HELSINKI

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

National guidance on research related to healthcare

Table 1

Examples of national guidance on research related to healthcare

Year	Source	Title
1979	US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research
1986	Royal College of Physicians (RCP), UK	Research Involving Healthy Volunteers
1988	Regulation, France	Law No. 88–1138 on the Protection of Persons agreeing to Biomedical Research ('Huriet Law')
1990	RCP, UK	Research Involving Patients
1991	Regulation, US	Code of Federal Regulations Title 45 Public Welfare Part 46 Protection of Human Subjects
1991	National Health and Medical Research Council (NHMRC), Australia	Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research

Table 1

Continued

Year	Source	Title
1992	Regulation, Finland	The Patient Rights Act (785/1992)
1992	Medical Research Council (MRC), UK	Responsibility in Investigations on Human Participants and Material and on Personal Information
1993	Medical Research Council of South Africa	Guidelines on Ethics for Medical Research (3rd edition)
1995	Ministry of Public Health, Thailand	Rule of the Medical Council on the Observance of Medical Ethics
1996	National Health Council of Brazil	Resolution No. 196/96 on Research Involving Human Subjects
1997	Health Research Council of New Zealand	Guidelines on Ethics in Health Research
1997	Medical Research Council of Canada	Code of Ethical Conduct for Research Involving Humans
1997	National Consensus Conference on Bioethics and Health Research in Uganda	Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda
1998	Committee on Research involving Human Subjects, China	Guidelines on Ethical Review of Medical Research
1998	Legislation, The Netherlands	Law of 26 February 1998, containing regulations with regard to medical-scientific research on humans
1998	MRC, UK	Good Clinical Practice in Clinical Trials
1998	MRC, UK	Interim Guidelines. Research Involving Human Participants in Developing Societies. Ethical Guidelines for MRC-sponsored Studies
1998	Health Research Council of New Zealand	Guidelines for Researchers on Health Research Involving Maori
1998	Medical Research Council of Canada/ National Sciences and Engineering Research Council of Canada/Social Sciences and Humanities Research Council of Canada	Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans
1999	Regulation, Finland	Decree on Medical Research (986/1999)
1999	NHMRC, Australia	National Statement on Ethical Conduct in Research Involving Humans
2000	Indian Council of Medical Research	Ethical Guidelines for Biomedical Research on Human Subjects
2000	Nepal Health Research Council	Ethical Guidelines for Biomedical Research Involving Human Participants in Nepal
2000	Clinical Trials Working Group of the South African Department of Health	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa
2001	National Committee for Ethics in Social Research in Health (NCESSRH) India	Ethical Guidelines for Social Science Research in Health
	Food and Drug Administration (US)	21 CFR 50: Protection of Human Subjects
	Food and Drug Administration (US)	21 CFR 56: Institutional Review Boards
	Agency for International Development (US)	22 CFR 225: Protection of Human Subjects

National and international guidance on specific topics in research related to healthcare

Table 2

Examples of national guidance on standards of care

Source	Country	Text
National Health Council of Brazil 'Resolution Nº 196/96 on Research Involving Human Subjects' (1996)	Brazil	'... the use of placebos, in terms of non-maleficence and of methodological requirement [must be fully justified] ...' **III.3 f**
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'Denial of the available treatment to control (placebo) group of patients is unethical.' **p. 27.** The use of a placebo as one arm of a trial in experimental epidemiological studies is not prohibited however. **See p. 35**
Clinical Trials Working Group of the South African Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	'It may be justifiable to use a placebo in communities that do not have access to interventions that are the standard care in resource-rich settings.' however '... the balance between potential harms and benefits should be such that the potential benefits to the community would considerably outweigh the harm.' **Paragraph 9.3.2** 'During and after a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values ... a subject [should be informed] when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.' **Paragraph 3.4**
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide adequate and safe medical ... care, where appropriate, to participants during the clinical trial ... and must ensure that appropriate medical care and follow-up procedures are maintained after the trial for a period of time that is dependent upon the nature of the disease, the trial and the intervention(s).' **V Procedures for the Investigation of New Drugs and Devices, D. Responsibilities of the Investigator, (3), p. 53** 'Placebo-controlled trials may be conducted (a) [where] based on knowledge ... available at the commencement of the trial, the new drug or device to be tested does not confer any significant benefit compared to the placebo, and (b) the placebo arm is provided with the treatment or diagnosis product or device considered to be the normal standard of care in the community in which the trial is being conducted'. **V Procedures for the Investigation of New Drugs and Devices, C. Justification of the Trials, (3) (a) and (b), p. 52**
Medical Research Council 'Interim Guidelines for Research Involving Human Participants in Developing societies – Ethical Guidelines for MRC-sponsored studies' (1998)	UK	Requires that the 'best proven ... method ... should take account of the available and feasible healthcare in the particular developing society'. **Specific considerations: Paragraph 6**
Royal College of Physicians 'Research involving Patients' (1990)	UK	'Where ... effective treatment is important for the future well being of the patient, ... a controlled trial [should] ... be undertaken only if, at the outset, the investigator does not know whether the trial treatment is more effective or less effective than the standard treatment with which it is to be compared ...' **Paragraph 7.99** However, 'Withholding effective treatment for a short time, whether or not it is substituted by a placebo, can sometimes be acceptable in order to validate a technique of measurement or confirm the sensitivity or discrimination of a therapeutic trial design.' **Paragraph 7.100**

Table 2

Continued

Source	Country	Text
National Bioethics Advisory Commission 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.' **Recommendation 2.2**

Table 3

Examples of national and international guidance on responsibilities for harm caused by research

Source	Country	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	International	'Some epidemiological studies may inadvertently cause harm. Monetary losses should be promptly repaid. Compensation is difficult when it is not appropriate to make monetary payments. Breach of confidentiality or insensitive publication of study findings, leading to loss of group prestige, or to indignity, may be difficult to remedy. When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation.' **Paragraph 47**
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Participants' (1993)	International	'Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death their dependants are entitled to material compensation. The right to compensation may not be waived'. **Guideline 13**
National Health Council of Brazil 'Resolution N° 196/96 on Research Involving Human Subjects' (1996)	Brazil	'The researcher, the sponsor and the institution must assume full responsibility for providing comprehensive care to the research subjects, as regards complications and injury resulting from foreseen risks.' **Paragraph V.5** 'Research subjects that suffer any type of injury resulting from their participation in the research, regardless of such injury having been foreseen in the terms of consent, or not, have the right to receive comprehensive medical care, as well as an indemnity.' **Paragraph V.6** 'Under no circumstance will the research subject be required to waive his/her right to indemnity for injury resulting from the research. The form used in obtaining the freely given and informed consent of the research subjects must not contain any clause exempting the researcher from responsibility or depriving any individual of his/her legal rights, including the right to seek an indemnity for injury resulting from the research.' **Paragraph V.7**
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'Each research shall include an in-built mechanism for compensation for the human subjects either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive after-care, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human subject and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.' **P. 9**

Table 3

Continued

Source	Country	Text
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide evidence of insurance to cover claims for injuries, disabilities, or death of a clinical trial participant that has resulted from participation in a clinical trial.' **V. D. (6)** 'The sponsor is responsible for providing compensation or indemnity in the event of trial-related serious injury, disability, or death, according to laws and regulations in effect at the time of the trial.' **V. E. (6)**
Royal College of Physicians 'Research Involving Patients' (1990)	UK	'Although the chances of harm coming to patients in the course of carefully conducted research are very small, it is important that proper arrangements are made to compensate patients in the event of such harm occurring.' **Recommendation 58** 'Bodies that sponsor research, including both publicly funded bodies ... and the pharmaceutical industry, should now so arrange their affairs as to implement the principle that injury due to participation in research sponsored by them or conducted by their staff with the approval of a Research Ethics Committee shall be compensated by a simple, informal and expeditious procedure.' **Recommendation 59** 'In the event of any significant injury the patient must be entitled to receive compensation regardless of whether there may or may not have been negligence or legal liability on any other basis.' **Recommendation 60**
National Bioethics Advisory Commission 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'The U.S. government should not sponsor or conduct clinical trials that do not, at a minimum, provide the following ethical protections...adequate care of and compensation to participants for injuries directly sustained during research ...' **Recommendation 1.1**

Table 4

Examples of national and international guidance on the composition of research ethics committees

Source	Country	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	International	Epidemiologists, other health practitioners and lay persons qualified to represent a range of community, cultural and moral values. Membership should be of diverse composition and include representatives of any populations specifically targeted for study. **Paragraph 36**
CPMP/ICH 'International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice' (1996)	International	At least one member should be a non-scientist and one member independent of the institution/trial site. **Paragraph 3.2.1**
United Nations Development Programme (UNDP), World Bank, World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) 'Operational Guidelines for Ethics Committees that Review Biomedical Research' (2000)	International	Should be multidisciplinary and multi-sectorial in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community. **Paragraph 4**

Table 4

Continued

Source	Country	Text
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	Chair should not be head of the institution and preferably drawn from outside the institution. Members should include a mix of medical and non-medical, scientific and non-scientific individuals and representatives of the lay public. The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. Diversity is important in terms of age, gender, community, etc. Members should be aware of local, social and cultural norms. Based on the nature of the research proposals, subject experts could be selected, along with specific patient groups as appropriate. Model membership would include: the Chair, 1-2 basic medical scientists, 1-2 clinicians from various Institutes, 1 legal expert or retired judge, 1 social scientist or NGO representative, 1 philosopher/ ethicist/ theologian, 1 lay person from the community and a Member Secretary. **P. 12–13**
South Africa Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	Members should be representative of the communities they serve and reflect the demographic profile of the population of South Africa. Both genders should be represented with no more than 70% of members coming from one of the genders. Membership should include at least one of each of the following: lay member, legally trained member, member with knowledge of, and current experience in areas of research that are regularly considered by the ethics committee, member with knowledge of and current experience in the professional care. counselling or treatment of people. **Paragraph 8.2**
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda'(1997)	Uganda	Members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Diversity should be demonstrated in terms of gender, region, religion and cultural backgrounds and sensitivity to issues such as community attitudes. Membership should allow for the acceptability of the proposed research to be ascertained in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice. Both sexes should be represented. The Committee must not consist entirely of members from one profession, tribe, religion or social or economic class and lack of formal education should not exclude an individual from membership. Membership should include at least one of the following however: member whose primary concerns are in scientific areas, member whose primary concerns are in non-scientific areas, member unaffiliated with the institution and not from the immediate family of a person affiliated with the institution. **11. A. 1–4**
Department of Health 'Ethics Committee Review of Multi-centre Research. Establishment of Multi-Centre Research Ethics Committees' (1997)	UK	Diverse composition reflecting a mix of gender, age and ethnic background and drawn from throughout the region the MREC serves. Membership should include: hospital medical staff, nursing staff, general practitioners, other NHS professional staff and lay persons. Health professionals should be mainly drawn from those actively involved in clinical care and those experienced in clinical investigation and research. **Paragraph 11**

Table 4

continued

Source	Country	Text
Department of Health 'Governance Arrangements for NHS Research Ethics Committees' (2001)	UK	Membership should consist of a mixture of 'expert' and 'lay' members, balanced in terms of age and gender and with ethnic minorities and the disabled represented. Expert members should have relevant methodological and ethical expertise, experience of clinical practice, statistics relevant to research or pharmacy. At least one third of membership should be comprised of lay members who are independent of the NHS. At least half of the lay membership should consist of persons who have never been either health or social care professionals or involved in carrying out research involving human participants, their tissue or data. Advice may be sought from specialist referees on relevant aspects of a research proposal where such lies beyond the expertise of the existing members. **Paragraphs 6.2–6.5, 6.7, 6.10**

Table 5

Examples of national guidance on what should be provided once research is over

Source	Country	Text
National Heath Council of Brazil 'Resolution No. 196/96 on Research Involving Human Subjects' (1996)	Brazil	Research involving human subjects, must whenever possible guarantee that: 'research in communities is translated into benefits whose effects continue to be felt after the research is concluded;' '... the individuals and communities where the research was undertaken [receive] a return on the benefits obtained in the research. When it is really beneficial to foster or encourage changes in practices or behaviors in the interest of a community, the research protocol must include, whenever possible, provisions to communicate such benefits to the individuals and/or communities' 'to ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents' 'to submit evidence, in case of research conducted abroad or with external cooperation, of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research...Studies sponsored by external organizations must also respond to training needs in Brazil, so that the country be able to independently develop similar projects.' **Paragraph III.3m,n,p,s**
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'After the clinical trial is over, if need be, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country.' **P. 27**
Clinical Trials Working Group of the South African Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	'Where a patient has a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long term provision of study drugs and of clinical monitoring, including the costs of medical staff.' **Paragraph 9.3.5** 'Research, which has direct public health implications, such as vaccine trials, require wide consultation. This should include discussions with South African Department of Health and the Medical Research Council so that implementation of study results can be addressed at an early stage.' **Paragraph 9.7.3**

Table 5

Continued

Source	Country	Text
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide assurances that, if the investigational product is found to be beneficial, the investigator will make every effort to ensure its provision, without charge, to participants in the trial following the conclusion of the trial. In addition, the investigator shall make a reasonable effort to secure the product's availability to the local community in which the research occurred.' **V.D.(4)**
MRC 'Guidelines for Good Clinical Practice in Clinical Trials' (1998)	UK	'The [Trial Steering Committee] should ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and due consideration is given to the implementation of the results into clinical practice.' **Paragraph 6.9.1**
NBAC 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.' **Recommendation 4.1** 'Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.' **Recommendation 4.2** 'Where applicable, U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing, reviewing, and conducting clinical trials in developing countries. Projects should specify plans for including or identifying funds or other resources necessary for building such capacity.' **Recommendation 5.6**

Guidance on the ethics of research related to healthcare available via the internet

International and regional guidance

CIOMS (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**
Available at: http://www.cioms.ch/frame_1993_texts_of_guidelines.htm

CIOMS (1991) **International Guidelines for Ethical Review of Epidemiological Studies**
Available at: http://www.cioms.ch/frame_1991_texts_of_guidelines.htm

Council of Europe (1997) **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine**
Available at: http://conventions.coe.int/treaty/en/treaties/html/164.htm

CPMP/ICH (1996) **Note for Guidance on Good Clinical Practice**
Available at: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf

UNAIDS (2000) **Ethical considerations in HIV preventive vaccine research. UNAIDS guidance document**
Available at: www.unaids.org/publications/documents/vaccines/vaccines/Ethicsresearch.pdf

WHO (1995) **Guidelines for good clinical practice (GCP) for trials on pharmaceutical products**
Available at: http://www.who.int/medicines/library/par/ggcp/GCPGuidePharmatrials.pdf

WHO (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**
Available at: www.who.int/tdr/publications/publications/ethics.htm

WMA (2000) **Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000**
Available at: http://www.wma.net/e/policy/17-c_e.html

National guidance

Agency for International Development (US) **22 CFR 225: Protection of Human Subjects**
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_99/22cfr225_99.html

Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks **Code of Federal Regulations Title 45 Part 46: Protection of Human Subjects**
Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

Food and Drug Administration (FDA) (US) **21 CFR 50: Protection of Human Subjects**
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr50_00.html

Food and Drug Administration (FDA) (US) **21 CFR 56: Institutional Review Boards**
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr56_00.html

Food and Drug Administration (FDA) (US) **21 CFR 312: Investigational New Drug Application**
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr312_99.html

Health Research Council of New Zealand (1997) **HRC Guidelines on Ethics in Health Research**
Available at: http://www.hrc.govt.nz/ethicgui.htm

Indian Council of Medical Research (2000) **Ethical Guidelines for Biomedical Research on Human Subjects**
Available at: http://www.icmr.nic.in/ethical.pdf

Health Research Council of New Zealand (HRC) (1998) **Guidelines for Researchers on Health Research Involving Maori**
Available at: http://www.hrc.govt.nz/Maoguide.htm

Medical Research Council (MRC) (UK) (1998) **Guidelines for Good Clinical Practice in Clinical Trials**
Available at: http://www.mrc.ac.uk/pdf-ctg.pdf

Medical Research Council (MRC) (UK) (2000) **Personal Information in Medical Research**
Available at: http://www.mrc.ac.uk/pdf-pimr.pdf

Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada (1998) **Tri-Council Policy Statement. Ethical Conduct for Research involving Humans**
Available at: http://www.nserc.ca/programs/ethics/english/ethics-e.pdf

Medical Research Council (South Africa) (1993) **Guidelines on Ethics for Medical Research, 3rd Edition**
Available at: http://www.mrc.ac.za/ethics/ethics.htm
(A 4th edition is being prepared and will be made available at: http://www.sahealthinfo.org/ethics/index.htm)

National Bioethics Advisory Commission (US) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**

- Volume I: Report and Recommendations of the National Bioethics Advisory Commission
- Volume II: Commissioned Papers

Available at: http://bioethics.georgetown.edu/nbac/pubs.html

National Health and Medical Research Council of Australia (1991) **Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research**
Available at: http://www.health.gov.au/nhmrc/issues/asti.pdf

National Health and Medical Research Council of Australia (1999) **National Statement on Ethical Conduct in Research involving Humans**
Available at: http://www.health.gov.au/nhmrc/publications/pdf/e35.pdf

National Health Council of Brazil (1996) **Resolution No. 196/96 on Research Involving Human Subjects**
Available at: http://www.aids.gov.br/resolution_196.htm

National Health Council of Brazil (1997) **Resolution No. 251/1997**
Available at: conselho.saude.gov.br/docs/CNS.Reso251.English.doc

National Health Council of Brazil (1999) **Resolution No. 292/1999**
Available at: conselho.saude.gov.br/docs/CNS.Reso292.English.doc

South African Department of Health (2000) **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa**
Available at: ftp://ftp.hst.org.za/pubs/govdocs/clinical.pdf

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (US) (1979) **The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research**
Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm

Appendix 2

Types of research design

Many different kinds of research related to healthcare take place in developing countries. These include:

- basic research
- clinical research
- epidemiological research
- social and behavioural research
- intervention studies, including clinical trials and community-based trials
- health services and operational research

Basic research is usually laboratory-based and includes studies at the cellular level, and of immunity and pathogenesis. Such research is often dependent on the use of samples from patients.

Clinical research is often conducted with patients in a medical setting, such as a hospital, and is designed to obtain better information on the natural history or pathogenesis of a condition that may lead to improved strategies for diagnosis, treatment or prevention of a disease.

Epidemiological research usually involves population-based investigations, which may be cross-sectional surveys of selected populations (case-control studies) or all members of a community, or may involve longitudinal study of a population over time (cohort studies). Such research is conducted to obtain an improved understanding of the natural history of a disease or to identify factors that increase or decrease the risk of disease in individuals. Often such investigations involve the study of large populations and they may be observational or interventional in nature. The aim is to identify strategies for the better prevention or treatment of disease, through an improved understanding of risk factors for disease or for progression of disease.

Social and behavioural research is often a component of epidemiological research and focuses on the study of behavioural and social factors that may modify risk of disease in individuals or in populations. Such research may involve the collection of sensitive information about a person and their lifestyle (e.g. sexual behaviour). While some forms of research may only involve observation others may involve studying or testing ways of changing behaviour or social circumstances.

Intervention studies are conducted to evaluate the impact of specific interventions on the prevention of disease, often in the context of community-based intervention trials, or in modifying the clinical course of disease, often in the context of clinical trials. Such research may provide the basis for policy decisions and priority setting. Intervention studies usually involve the comparison of different treatment or prevention strategies in which the current intervention method is compared with another method, often new, that may be more efficacious than the existing intervention. If there is no existing effective intervention, a placebo or 'no intervention' may be used as the comparison against which to assess the impact of the new intervention. Ideally, individuals are randomly allocated to receive the different interventions being compared in the trial.

Health services and operational research are concerned with the study of methods of delivery of healthcare, access to treatment and quality of care, with the aim of finding improved methods that lead to better care. Such studies often include an evaluation of the cost of providing the intervention and the benefit it provides.

Appendix 3

Issues to be considered when reviewing research proposals

Policy issues

- Does the research need to be conducted in the particular country under consideration?
- Can the purpose of the research be justified? Is the proposed research relevant to national priorities for healthcare-related research? If the research is not relevant to the national priorities, is it nevertheless justified?
- Have the criteria for selecting the study population been outlined? Have any issues related to the gender of the study population been considered?
- Is the funding which has been allocated sufficient to complete the project?
- If favourable, could the results be implemented, either now or in the foreseeable future? If not, does the research have any beneficial secondary or indirect effects (e.g. the development of expertise in research)?

Scientific issues

- Is the researcher undertaking the research appropriately qualified and does he or she have the relevant experience?
- Is the researcher available for the duration of the study?
- Are the staff supporting the research and the facilities available, including technical facilities, adequate?
- Is this the first time this type of research has been conducted? If not, has the scientific value of undertaking the research been justified?
- Is the research design appropriate? Is it likely to yield an unambiguous answer to the research questions which have been posed?
- Is it possible for the quality control of data and analysis to be achieved?
- Has consideration been given to issues associated with biosafety and good manufacturing practice?
- Can the diagnostic, therapeutic and preventative interventions be handled safely?
- Is a control group being used in the research? If so, have details been included in the proposal of the treatment that will be given?
- Will there be any form of follow-up for participants in research? If so, have details of this been provided?

Ethical issues

- Has the research received appropriate scientific review?
- Has the project been given approval by an ethics review committee in the host/sponsoring country?
- Have any efforts been made to consult with the relevant communities during the course of designing the research?

- Have details been given of the measures to be used to recruit prospective participants in research?
- Has consideration been given to who will benefit from the research?
- Has consideration been given to the risks involved in undertaking the research? Have measures been taken to minimise risks to participants? Is there adequate provision for monitoring the data collected to ensure the safety of subjects?
- Have details been given of the information that will be made available to prospective participants? Is this appropriate and complete? Is it in a language and at a level of complexity appropriate to prospective participants in research?
- Have details been given of the procedure that will be used to obtain assent at the level of institutions and communities, where appropriate?
- Have details been given of the procedure that will be used to obtain consent from individual participants? Is it appropriate to ask participants to sign a consent form? If not, how will their consent be recorded? Where verbal consent to research is anticipated, is there an appropriate process for witnessing the consent?
- Have provisions been made for receiving and responding to queries and complaints from participants in research or their representatives during the course of a research project?
- Have details been given of who will be given access to the personal data of the participants in research, including medical records and biological samples? Are measures being put in place to maintain confidentiality and are these adequate?
- Are the standards of care being proposed acceptable? Are they appropriate for the country in which the research is being conducted?
- Are there other research designs which could answer the research question being posed? If so, why has this particular design been proposed?
- Is a control arm to be used? If so, has its use been properly justified? If it is being proposed that the control group in the research should receive less than a universal standard of care, has this been justified? Have details been given of how the intervention will be allocated? Have details been included of what information participants in the control group will be given?
- Have any plans to withdraw or withhold standard therapies for the purpose of the research been justified?
- What standard of care will be provided for participants who develop diseases or conditions other than those being studied? If it is something less than the best intervention available as part of the national public health system, has this been justified?
- Will research participants be offered payment, gifts or other inducements in return for their participation? Are these appropriate?
- Will there be follow-up and long-term review of the research? If so, have details been given of how this will be carried out?
- Have provisions been made for compensation or treatment in the case of death or injury to research participants?
- Have researchers endeavoured to secure post-trial access for effective interventions for participants in the trial? If not, has the lack of any such arrangements been justified?
- Has consideration been given to the possibility of introducing an intervention shown to be successful to the wider community and maintaining its availability? If it is not thought possible to make the

intervention available to some or all of the population in the country in which the research is to be conducted, can the research be justified?

- Will regular progress reports be made to the research ethics committee? If so, have details been given of how frequently these will occur? Have details been given of any arrangements that have been made for providing proper documentation to the committee?
- Have details been given of how the results of the research will be used? How will the results of the research be disseminated to participants and other interested parties?
- Does the research include provisions for the development of expertise in research within the developing country in which it is to be conducted? If not, is the lack of such provisions justified?

Research conducted with vulnerable populations

- Has the inclusion of individuals in research who cannot consent been justified?
- Is the research question posed important to the health and well-being of this vulnerable population?
- Is the research design appropriate?
- Have safeguards been built into the research design to prevent undue coercion or influence of this group?

Appendix 4

Fact-finding meetings

The Working Party is very grateful to the following individuals[1] for taking the time to meet with members of the Working Party and for providing insights into issues relating to externally-sponsored research in developing countries.

London, UK, 10 April 2000
Dr Gill Samuels, Pfizer (UK)

London, UK, 6 June 2000
Professor Daniel Wikler, Staff Ethicist, World Health Organization (WHO)

Oxford, UK, 17 September 2000
Professor Don Bundy, International School Health Initiative, The World Bank, US
Dr PK Das, Vector Control Research Centre, Pondicherry, India
Dr Nick Day, Centre for Tropical Medicine, University of Oxford, UK
Professor Charles Kihamia, UKUMTA (Tanzania Partnership for Child Development), Dar es Salaam, Tanzania
Dr Martin Meremikwu, Department of Paediatrics, College of Medical Sciences, University of Calabar, Nigeria
Dr Petri Ruutu, Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre, London, UK
Dr Lorenzo Savioli, Strategy Development and Monitoring for Parasitic Diseases and Vector Control and Communicable Diseases Control, Prevention and Eradication, World Health Organization, Geneva, Switzerland
Professor Thor Theander, Institute for Medical Microbiology and Immunology, Panum Institute, University of Copenhagen, Denmark
Dr Bill Watkins
Professor Nick White, Wellcome-Mahidol University Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine, Mahidol University, Bangkok

London, UK, 6 December 2000
Professor Alan Maynard, University of York

Chennai, India, 21 January 2001
Dr Rani Balasubramanian, Tuberculosis Research Centre (TRC), Chennai
Professor MK Bhan, All India Institute of Medical Sciences, Delhi
Professor George Chandy, Christian Medical College (CMC), Vellore
Professor NK Ganguli, Indian Council of Medical Research (ICMR)
Dr M Gupte, National Institute of Epidemiology
Professor Ravi Jacob Korula, CMC, Vellore
Dr MS Jawahar, TRC, Chennai
Dr L Kameshwaran, Former President, National Academy of Medical Sciences
Dr C Kolapp, TRC, Chennai
Professor R Korula, CMC, Vellore,
Justice Krishnaswamy
Dr Nandini Kumar, ICMR
Dr V Kumaraswami, TRC, Chennai
Dr HN Madhavan, Vision Research Foundation, Chennai
Dr MK Mani, Consultant Nephrologist, Chennai
Dr Rema Mathew, TRC, Chennai
Dr Vasantha Muthuswamy, ICMR
Dr MUR Naidu, The Nizam's Institute of Medical Sciences

1 Institutional affiliations at the time of the meeting are listed

Dr PR Narayanan, TRC, Chennai
Dr S Rajasekaran, TRC, Chennai
Dr Rajeswari Ramachandran, TRC, Chennai
Dr VD Ramanathan, TRC, Chennai
Dr Ravi Rengachari, ICMR
Dr K Sadacharam, TRC, Chennai
Dr MA Salam, The Centre for Health and Population Research (ICDDR-B), Bangladesh
Dr DK Sampath
Professor KR Sethuraman
Professor CH Shashindran, Department of Pharmacology, Pondicherry
Dr H Srinivasan
Dr VK Srinivasan, Indian Institute of Economics
Professor Manorama Thomas, Professor of Anatomy and Human Genetics, Bangalore
Professor Yogesh Tripathy, Kasturba Medical College
Dr KC Umapathi, TRC, Chennai

Boston, US, 22 March 2001
Professor George Annas, Boston University
Professor Barry Bloom, Harvard School of Public Health
Dr Chris Howson, March of Dimes
Professor Robert Levine, Yale University
Professor Ruth Macklin, Albert Einstein College of Medicine

Washington DC, US, 23 March 2001
Dr Finley Austin, Roche
Dr Melody Lin, Office for Human Research Protections (OHRP)
Dr Peter Lurie, Public Citizen
Dr Eric Meslin, National Bioethics Advisory Commission (NBAC)
Mr Paul Ndebele, Johns Hopkins University
Dr Godwin Ndossi, Johns Hopkins University
Dr Duncan Ngare, Johns Hopkins University
Ms Alice Page, NBAC
Ms Maureen Power, National Institute of Allergy and Infectious Diseases (NIAID)
Dr Regina Rabinovitch, Malaria Vaccine Initiative (MVI)
Sara Radcliffe, Pharmaceutical Research and Manufacturers of America (PhRMA)
Dr Gillian Woolet, PhRMA

London, UK, 13 June 2001
Dr Imogen Evans, Medical Research Council (MRC) UK
Dr Richard Lane, The Wellcome Trust

Appendix 5

Method of working and consultation

The Working Party met nine times between January 2000 and September 2001. A consultation with the public was held between July 2000 and January 2001 when organisations and individuals with an interest in the topic were invited to comment on the issues raised by research related to healthcare in developing countries. A total of 70 responses were received from over 20 different countries. Respondents included a number of relevant organisations such as sponsors of research, research ethics committees and the pharmaceutical industry, and individuals with expertise in ethics, law, medical research and health policy. Those who responded are listed below and the Working Party is grateful to them all. Some of the main themes to emerge from the consultation responses are set out below.

What kind of research is most beneficial to developing countries?

There was unanimous agreement that research in developing countries should be related directly to the health problems of those countries, and that it should focus on diseases that affect the developing world. Eleven respondents specifically mentioned that it was unacceptable that 90% of the global funds for research related to healthcare was spent on 10% of the population. Some respondents also suggested that a range of research should be carried out, with both short- and long-term benefits, such as basic research into causes and mechanisms of disease, and their diagnosis and treatment. It was also considered important that developing countries were encouraged to define their own research priorities and that partnerships should be developed between those countries hosting and those sponsoring the research. It was also considered very important that the results be made available to the country and community in which the research took place.

In response to the question whether it was morally acceptable for research to be conducted in a developing country when it could also be conducted in a developed country, the majority of respondents considered that it was acceptable, but only if the research was of benefit to those in the developing country. It was generally thought to be unacceptable if research was conducted in a developing country simply because it was cheaper or easier to do so or because of a fear of litigation or a fear of hostile public opinion. However, the view was also expressed that it would be wrong to deny those in developing countries the opportunity to take part in research which offers some direct and indirect benefits. Additionally, it was pointed out that it was sometimes necessary to repeat research in developing countries to determine how effective an intervention might be in the local environment.

One type of harm that might be caused by research related to healthcare in developing countries was the raising of unrealistic expectations of what would be provided to participants once the research was over. Other issues were similar to those faced in developed countries, for example what should happen if participants were harmed as a result of taking part in research and whether compensation would be available for injuries arising from research. A few respondents raised concerns that a lack of infrastructure in developing countries could increase risks associated with research. Others thought that externally-sponsored research might lead to the exploitation of poor and vulnerable populations by more wealthy and powerful ones.

Cultural issues

Consent

The issue of informed consent received the most attention from respondents. It was generally felt to be essential that cultural practices should be recognised in the consent process. Accordingly, the consent process should be flexible and should respect local practices. The majority of respondents thought that although community assent should be sought as well as individual consent, community assent should not be accepted as a substitute for individual consent. Respecting the autonomy of an individual was of

overriding importance. Respondents noted the importance of confidentiality and anonymity for individuals who wished to decline to participate in research, so they did not feel pressured to participate in the research by the community. It was also noted that not all cultural practices were widely supported by those who were subject to them. Some practices were unpopular with people who did not have the power to change them and researchers should be aware of this.

Consent could be obtained either verbally or in writing, but it was noted that signing the consent form was less important than ensuring that participants understood what was involved in the research. Some respondents thought that the benefits of research were often overemphasised, and stressed the importance of making sure that the participants understood the risks involved in the research.

Some respondents noted that it was sometimes difficult to provide adequate information to participants in local languages, particularly when concepts such as placebo and randomisation were unfamiliar. To explain such information required sensitivity and appropriate education.

Alternative therapies

Several respondents noted that many prospective research participants consult traditional healers, or use traditional therapies. It was important to be aware of this behaviour so that research could be set in the appropriate context and any conflicts between the research and traditional therapies could be addressed. Alternative therapies had the potential to influence research results due to real effects or placebo/psychological effects and also posed a challenge in the management of interactions/ interference from traditional herbal 'remedies'.

Key ethical issues

Respondents considered that key ethical issues to be addressed in research included autonomy, protection of human rights, respect for persons, beneficience, non-maleficience and justice. It was also considered unacceptable to exploit prospective participants in developing countries for the benefit of those in developed countries. A few respondents suggested that each culture should be able to determine their own ethical framework to apply to research. Others stated that the ethical framework should be the same in developed and developing countries. In particular, it was considered that the balance of benefit and risk to individuals and to the society should depend on the local values of the society.

Inducements to participate in research

Respondents agreed that it was important to show that participants' contribution to research was valued, but differed about how best to do this. One-fifth of respondents suggested that participants should be recompensed for time and loss of earnings. There was a feeling that it was important to de-emphasise financial benefits of participating in research whenever possible and that cash payments should be avoided. Indirect inducements, such as the provision of healthcare, food, education or baby-care items were considered to be acceptable alternatives. The provision of healthcare for children was considered to be particularly appropriate. It was thought that ideally an enduring commitment to the community should be given.

Other respondents took the view that any inducements to participate in research should be sensitive to the context in which the research was conducted. In such circumstances local opinion, including the views of local research ethics committees, should determine if an inducement was acceptable. It was noted that in some communities even offering a meal might amount to a significant inducement to participate in research.

An inducement was considered to be unacceptable if it was so large that a participant would be prepared to assume risks that would otherwise be deemed unacceptable. However, it was pointed out that it would be almost impossible to enforce any rule concerning inducements. One suggestion was that researchers should be liable to a penalty in the event of an unacceptable inducement being offered.

Standards of care

Issues concerning the appropriate standard of care that should be provided during research produced a wide variety of opinions amongst respondents, with no clear division of views between particular types of organisations or between regions of the world.

Many respondents felt that the locally appropriate standard of care should be taken into account. One reason given was that the use of local standards was important for the results of the research to be relevant to the local context. Additionally, providing standards of care comparable to those available in a country sponsoring the research could cause severe imbalances in the level of healthcare available in differing communities within developing countries. In addition, there may be difficulties in sustaining such standards of care beyond the completion of the research. An additional concern was that requiring the standard of care available in a developed country might prevent valuable research from taking place.

However, other respondents took the view that a universal standard of care should be provided. Some respondents thought that research participants should receive the optimal standard of care generally available to those in the community in which the research was to be conducted. Where no treatment was available for a condition, the standard of care available in the sponsoring country should be used.

A compromise that was suggested was that the decision about the standard of care to be used in a specific research project should be made on a case-by-case basis, depending on the local situation. Every effort would need to be made to improve the circumstances under which research took place, and to help improve the local healthcare services for the future.

Current guidance

Overall it was felt that the current guidance on research provided adequate safeguards although the interpretation of some of the guidance was subject to debate. It was noted that it was difficult to enforce the international guidance. Rather than producing new guidance, it was suggested that it would be more useful to increase awareness of the existing guidelines, improve their dissemination and strengthen capacity for their implementation.

There were differing views concerning the need for an additional international regulatory agency to oversee the implementation of guidelines. Some respondents felt this would be helpful, and suggested that such a body could help resolve conflicts of interest. However, others felt that an additional agency would be unlikely to provide substantial help and would not be feasible. It was suggested that a central ethical evaluation committee of an existing body such as the World Health Organization (WHO) should resolve conflicts of interpretation of guidelines.

Respondents from research ethics committees had a number of comments on the guidelines, and in particular the scrutiny of research projects. One suggestion was that externally-sponsored research should receive a form of international review followed by local review in the countries where the research would be conducted. An alternative was to have teams of regional adjudicators licensed by WHO. A third suggestion was for the establishment of partnerships between research ethics committees in the UK and emerging ethical review committees in the developing world to share experience and expertise. Some assessment of proposed research by an organisation that was open to public scrutiny

and conformed to international standards was thought to be important. However, there were differing views about the need for a further international regulatory agency.

Local research ethics committees

Most respondents stressed the need for local research ethics committees, which had an understanding of local customs and traditions. It was considered that these local committees needed to receive adequate training and support to equip them with the necessary knowledge and skills to conduct effective review. It was also important to ensure that different groups of people are adequately represented on such committees. National research ethics committees were thought to have an important role to play and should be encouraged.

It was noted that local research ethics committees were highly susceptible to conflicts of interest, differential relations in terms of power and political exigencies. Particular issues that needed to be addressed were the restraint of influence of prestigious researchers and independence from financial incentives from foreign sponsors.

What happens once research is over

The most common response to the consultation was that interventions shown to be successful should be provided after research to all the participants involved in the study. However, some respondents raised issues about the viability of this approach, noting that, for example, there might not be a mechanism to ensure the correct delivery of a medicine in the longer term. It was considered to be probably inevitable that standards of healthcare would fall once research was complete, but that any phasing out of treatments should be carefully planned in advance. Most importantly, it was suggested that issues related to what happens once the research was over should be addressed in the study design and funding proposals.

Two respondents argued that continuation of a treatment following research was not a requirement in developed countries, and so raised the question whether it should be a requirement in developing countries. Respondents from pharmaceutical companies were concerned that if it was required that a treatment shown to be successful was provided to all of those who needed it within a country, research which might be of benefit to developing countries could not be conducted.

Respondents considered that researchers had an ethical obligation to undertake long-term surveillance of populations who received preventive treatments in research in order to study long-term effects. This was considered to be important for both scientific and ethical reasons, particularly if the preventive treatment being studied might increase the risk of acquiring a disease later in life.

The costs of ongoing provision of treatment

Respondents thought that sponsors of research from the pharmaceutical industry and the public sector, in addition to national governments and other public authorities had some responsibility for the ongoing provision of treatment shown to be effective. Ultimately, it was suggested that the national and local governments held responsibility for the delivery of adequate healthcare to a population. The role of pharmaceutical sponsors was less clear. Some respondents suggested that the pharmaceutical industry should bear all or most of the cost of providing treatment on an ongoing basis, other respondents thought that the industry should be responsible only for providing treatment while the medicine was under licence, while others felt that the industry could not be expected to have a long-term obligation

beyond the period of the research. Genuine partnerships between those involved in sponsoring and conducting research and in providing healthcare were seen to be of importance. Respondents agreed that the provision of a therapy shown to be effective should be discussed prior to the start of any trial.

Is it acceptable to allow research in a community that cannot afford the treatment being tested?

There were differing responses to the question of whether it was acceptable to allow research in a community that could not afford the treatment being tested. Some respondents felt strongly that it was not acceptable under any circumstances. Others felt that the issue of whether or not a treatment could be provided on an ongoing basis was essentially a separate political and economic issue. It was proposed that developing countries should be entitled to decide for themselves whether or not to conduct such research, rather than being excluded on the grounds that they could not afford the treatment. Some diseases only occurred in the developing world and it was thought important not to restrict research into treatments for such diseases on the ground that such treatments could not currently be afforded. It was also suggested that there was no simple answer to the question of whether such research should be conducted, because the cost of a medicine might change, or special prices could be negotiated. Alternative routes for support and supply of a treatment should be considered in the early stages of planning a trial.

Responses to the public consultation

The Working Party wishes to thank the following individuals and their organisations for providing helpful information and insights into the subject of research related to healthcare in developing countries.

Organisations

Association of the British Pharmaceutical Industry (ABPI)
Association of Medical Research Charities (AMRC)
British Union Conference of Seventh-Day Adventists
The Church of England Board for Social Responsibility Science, Medicine and Technology Committee
Glaxo Wellcome plc
HIV/AIDS Vaccine Ethics Group (HAVEG), University of Natal, South Africa
MRC UK
Local and multicentre research ethics committees:

- West Berkshire
- South Birmingham
- Blackburn, Hyndburn & Ribble Valley
- Bolton
- Bradford
- Bromley
- Fife Health Board
- Glasgow Area Dental Ethics Committee
- Gwent
- Hartlepool
- North Allerton
- North Nottinghamshire

Oxford Psychiatric Research Ethics Committee
Plymouth
Salisbury
South Sheffield
South East Staffordshire
Trent multicentre research ethics committee
Ulster University
National Consumer Council
Royal College of Physicians
SmithKline Beecham
Swiss Academy of Medical Sciences Central Ethics Committee
The Wellcome Trust

Individuals

Dr Mohammed Abdus Salam, ICDDR-B, Bangladesh
Professor Adolfo Alvarez
Professor Solomon Benatar, University of Cape Town, South Africa
Dr David E Bratt
Professor Cheryl Cox Macpherson, St. George's University School of Medicine, West Indies
Dr John Dada, Fantsuam Foundation, Nigeria
Professor Bernard Dickens, University of Toronto, Canada
Dr Mike English, Wellcome Trust Research Laboratories, Kenya
Professor EM Essien, University of Port Harcourt, Nigeria
Dr Tamas Fenyvesi, Semmelweis University, Hungary
Professor David Fidler, Indiana University, US
Sitaleki A Finau, University of Auckland, New Zealand
Professor Brian Greenwood, London School of Hygiene and Tropical Medicine, UK
Dr Hemamal Jayawardena, United Nations Population Fund (UNFPA), Sri Lanka
Dr Anatoli Kamali, MRC Research Programme on AIDS in Uganda
Hyo Yoon Kang, European University Institute, Italy
Dr Monica Konrad, University of London, UK
Maureen A Kuyoh, University of Southampton, UK
Angela Kydd
Dr Klaus Lindpaintner, F Hoffman-La Roche
Dr Fernando Lolas, Pan-American Health Organisation (PAHO), Chile
Professor Adetokunbo Lucas, Harvard School of Public Health, US
Dr Dilys Morgan, MRC Research Programme on AIDS in Uganda
Dr Kamran Niaz, United Nations International Drug Control Program (UNDCP), Iran
Dr Pinyupa Plianbangchang, Naresuan University, Thailand
Dr RP Sapru, India
Dr SK Sharif, Provincial Medical Officer/Chief Medical Specialist, Kenya
Dr André Soton, Centre for Regional Development, Benin
Professor Dominique Sprumont, University of Neuchâtel, Switzerland
Professor B Vrhovac, University Hospital Medical School, Zagreb, Croatia
Dr Paul Wangai, Kenya Medical Association, Kenya
Angela Wasunna, The Hastings Center, US
Dr Jimmy Whitworth, MRC Research Programme on AIDS in Uganda

Glossary

African Trypanosomiasis

Also known as sleeping sickness, African Trypanosomiasis is a potentially life threatening parasitic disease. The parasites, *Trypanosoma*, are transmitted to humans by tsetse flies. The early stages of the disease are characterised by fever, headaches, pain in the joints and itching. When the parasite crosses the blood-brain barrier and enters the central nervous system, the disease moves into the neurological phase. This is when the characteristic signs and symptoms of the disease appear: confusion, sensory disturbances and poor co-ordination. An additional symptom is disturbance of the sleep cycle, which gives the disease its name. If treatment is not given prior to onset of the neurological phase, neurological damage is irreversible even after treatment.

AIDS (Acquired immune deficiency syndrome)

A disease caused by retroviral infection by the human immunodeficiency virus (HIV-1, HIV-2), that causes immune system failure and debilitation and is often accompanied by infections such as tuberculosis. The disease is transmitted through direct contact with bodily fluids (e.g. blood-blood or via sexual intercourse).

Albendazole (see also *Zentel*)

An oral medicine used to treat a variety of worm infections.

Antibody

A class of proteins of the immune system which react with and neutralise specific foreign antigens (any substance recognised by the immune system as 'non-self').

Antimycobacterial chemotherapy

Medical treatment for diseases caused by the bacteria *Mycobacterium*, such as tuberculosis and leprosy.

Antiretroviral

A group of medicines used in the treatment of HIV/AIDS.

Artemether

An antimalarial medicine administered intramuscularly.

Ayurveda

Ayurveda means 'the knowledge needed for long life' and is concerned with instruction on personal conduct, including diet, exercise and cleanliness, on keeping the body-soul in equilibrium, and on the diagnosis and treatment of various diseases. Health is maintained and restored through use of herbs,

ointments, enemas, massage and surgery and by attention to balanced levels of food, sleep, exercise and medical ingestion.

Azithromycin (see also *Zithromax*)

An antibiotic medicine commonly used to treat respiratory tract infections, infections of the skin and soft tissues and some sexually transmitted diseases.

Cancer

A disease where cells grow out of control and invade, erode and destroy normal tissue. There are over 200 different types of cancer that can occur anywhere in the body, with different causes and different symptoms.

Carrier state for infectious diseases

When a person harbours disease-causing micro-organisms and can transmit infection to others, though he/she is healthy and without clinical symptoms, he/she is said to be in a carrier state.

Cerebrospinal meningitis

Cerebrospinal meningitis or meningococcal meningitis is a contagious disease caused by the bacteria *meningococcus*. It occurs in both sporadic and epidemic outbreaks, predominantly in children and young adults. The disease is characterised by inflammation of the meninges (three layers of connective tissue that envelop the brain and spinal cord); the symptoms include severe headache, photophobia (light sensitivity) and neck stiffness. The disease can be severe with high mortality rates, or result in permanent neurological disability.

Chloramphenicol

A potent antibiotic which is normally used to treat life threatening infections, particularly those caused by *Haemophilus influenzae* and typhoid fever.

Clinical research and clinical trials (see also *Appendix 2*)

Medical research studies designed to answer scientific questions and to find better ways to prevent, detect, or treat disease. A large number of clinical trials are confined to testing the safety and efficacy of new medicines. There are four separate phases of such trials:

Phase I trials

Phase I studies will be the first time human subjects are exposed to the potential novel medicine. The objectives behind the study will be to investigate pharmacodynamics, dose-response, and in the case of vaccines, immune response, and to determine the maximum dose that can be tolerated by participants. In the case of most new medicines these studies will be undertaken in a small number of healthy

volunteers. It is not expected that evidence of efficacy of the medicine will be provided by Phase I studies.

Phase II trials

Using the information regarding the safe dosage range obtained from the Phase I studies, the compound will be administered to patients suffering from the target disease and now significant numbers of individuals will be recruited into the trial. Almost always these trials will be conducted in a number of clinical centres. The objective of the Phase II studies will be to seek evidence of the efficacy of the medicine against the specific disease. More information about the safety of the medication will emerge from these studies as larger numbers of individuals are exposed to it. In Phase II trials the patient will often be randomly assigned to the novel treatment group or to a group receiving a placebo (a compound possessing no therapeutic effect) or, more usually, a conventional and established treatment.

Phase III trials

Where a compound has shown evidence of efficacy without significant side effects it will enter Phase III trials in which many hundreds, or sometimes a few thousand patients will be enrolled. These trials will generally seek not only to confirm the clinical efficacy of the novel compound, but also to establish its efficacy in comparison with existing treatments. These studies will often be multicentre and sometimes undertaken on an international basis. Again, careful attention is paid to possible side effects as larger numbers of patients are exposed to the intervention. The end-points for Phase III studies include the demonstration of a statistically significant improvement in the efficacy of the novel medicine over the established therapies, if any such exist.

Phase IV trials

Once a new medicine reaches the market it will be subjected to post-marketing surveillance in order to identify side-effects and other adverse effects which would only become evident as much larger numbers of individuals are treated with. In addition, formal clinical trials continue in order to develop a greater understanding of the compound and its effects in a wider clinical environment, but also to extend its use for other indications or for different patient groups, such as children or the elderly. Special study designs may be used according to the objectives of the study to evaluate safety or efficacy. These may include study of temporal trends, case-control studies, or the phased introduction of an intervention in different areas. Phase IV studies may also be designed to measure the impact of the intervention on the epidemiological pattern or transmission of an infectious disease.

Communicable diseases (see also *non-communicable diseases)*

Communicable or infectious diseases are caused by living organisms, mainly micro-organisms (e.g. viruses, bacteria and fungi and groups intermediate between viruses and bacteria e.g. chlamydiae). The source of disease can be another human, animal or insect. Transmission occurs via several routes (e.g. physical contact, food and drink) and organisms typically enter the body by inhalation or direct contact.

Compulsory licensing

A legal intervention to restrict the monopoly rights of existing patent holders and make generic medicines or diagnostics (e.g. clinical tests) more available.

Conjugate

Paired together, such as in pneumococcal conjugate vaccines for pneumonia and meningitis.

Control

A control group in clinical research and clinical trials (see *clinical research and clinical trials*) contains participants who are not given the intervention which is being tested in the research and compared with a group who are given the intervention. In clinical trials, the intervention would normally be a novel treatment, such as a medicine or vaccine but interventions may also be social and behavioural in nature, for example, safe sex campaigns.

Diarrhoeal disease

Any group of diseases causing diarrhoea as the main symptom, i.e. an abnormal increase in the frequency and/or liquidity of the stools, which in developing countries (particularly in children) may be fatal.

Eflornithine

An antiprotozoal medicine used to treat African trypanosomiasis (sleeping sickness) (see *African trypanosomiasis*).

Elephantiasis

Gross swelling, usually affecting the legs and genitalia caused by chronic lymphatic obstruction by filarial worms (see *Lymphatic filiariasis*).

Epidemic

A temporary increase in the prevalence of a disease within a specific community or region. The rise in prevalence may last a few weeks or years.

Epidemiological research (see *Appendix 2*)

Research concerned with describing and explaining the occurrence of disease in populations.

Generic medicines

Generic medicines are chemically the same as brand name medicines. They have the same characteristics (e.g. intended use, dosage, route of administration, safety, and quality) but are typically much lower in price than their branded counterparts.

GNP (gross national product) per capita

GNP per capita reflects the average income of a country's citizens. It is calculated by dividing the final output of a country's goods and services in a year by the country's population.

GOBI-FFF

Growth monitoring, oral rehydration, breastfeeding, immunisation, food supplementation, family planning, and female education.

A programme of simple and inexpensive methods aimed at reducing child mortality.

Goitre

An enlargement of the thyroid gland, caused primarily by stimulation of the gland by the thyroid-stimulating hormone (TSH). This can be produced by iodine deficiency and excess or by certain foods and medications.

Hepatitis B

A virus transmitted through body fluids by poor surgical sterilisation procedures, close contact, blood contamination, infection at birth, needle sharing or sexual contact. It causes an acute illness, which may develop into chronic hepatitis. Symptoms include tiredness, sickness, fever, loss of appetite, stomach pains, and diarrhoea. Symptoms may also include dark yellow urine, and yellowish eyes and skin (also called jaundice).

Hepatitis E

A virus transmitted by faecal or oral routes, causing an acute resolving illness marked by inflammation of the liver and jaundice. It may be fatal during pregnancy.

Hib disease

Hib disease is a group of diseases caused by the *Haemophilus influenzae* type b bacteria e.g. pneumonia and bacterial meningitis.

Hib polysaccharide – protein conjugate vaccine

A vaccine for *Haemophilus influenzae* type B containing a "weak" polysaccharide (complex naturally occurring carbohydrates e.g. starch) linked to a protein.

Hippocratic oath

The oath attributed to the Greek physician, Hippocrates who is known as the father of medicine, which doctors have traditionally taken upon graduation, on the duties, obligations, and ethics of practising medicine.

Hydroxyurea

An anti-cancer medicine, used mainly in the treatment of chronic myeloid leukaemia (a cancer of the myeloid leucocytes, a type of white blood cell). Used in conjunction with anti-HIV medicines, it may also improve their efficacy in treating HIV infection.

Hypertension (anti-hypertensives)

Persistently high arterial blood pressure, which may have no known cause or be associated with other diseases. Hypertension is a risk factor for the development of diseases such as heart disease and stroke.

Infectious diseases

See *communicable diseases*.

Ivermectin

One of a class of medicines used to treat infestation with several species of nematode worms transmitted by biting insects. It is used as the medicine of choice for the treatment of onchocerciasis.

Leishmaniasis

A parasitic disease caused by the protozoa *Leishmania*, transmitted by the bite of some species of sand fly. Various forms of the disease are known, depending on the species of parasite. One form is visceral leishmaniasis, characterised by fever, enlargement of the spleen and liver, and anaemia. Symptoms typically develop over months, but can take years following infection. Most cases of visceral leishmaniasis occur in Bangladesh, Brazil, India, Nepal, and Sudan.

Leprosy

A chronic infectious disease caused by the bacteria *Mycobacterium leprae*. The disease mainly affects the skin and the peripheral nerves. The precise mode of transmission remains uncertain, but is from person to person, and close and prolonged contact is thought to be necessary.

Low dose spiral computed tomography

Computed tomography (CT) is a method by which an X-ray image of a cross-section of the body or head is reconstructed electronically and displayed. Low dose spiral computed tomography is a type of CT useful in the early detection of cancers, especially peripheral lung cancer.

Lumbar puncture

An invasive diagnostic test in which a needle is injected into the lower part of the spine canal to extract cerebrospinal fluid (CSF) for examination. This is used to diagnose, or rule out, certain diseases such as meningitis.

Lymphatic filariasis

Lymphatic filariasis is a parasitic disease caused by a worm transmitted by certain kinds of mosquitoes. Worms accumulate in the lymphatic system and may cause gross swelling of the legs (elephantiasis), and scrotum (hydrocoeles) and other body areas.

Magnetic resonance imaging (MRI)

A technique used to image internal structures of the body, particularly the soft tissue.

Malaria

Malaria is a tropical, parasitic disease transmitted by Anopheline mosquitoes. Symptoms include fever, shivering, pain in the joints, headache, repeated vomiting, generalised convulsions and coma. Left untreated, the disease may result in death.

Malarone

An anti-malarial medicine.

Measles

An acute infectious viral disease which, in Western urban communities, prior to the introduction of immunisation programmes, largely affected children. Immunisation programmes resulted in the incidence shifting to the unimmunised young adult population. The disease is characterised by symptoms such as a rash usually beginning in the mouth, high temperature, headache, and photophobia (light sensitivity). The disease is normally self-limiting but complications can occur through secondary infection (e.g. pneumonia) and the disease still has high mortality rates in the developing world.

Mefloquine

An anti-malarial medicine, particularly used in areas of the world where there is a high risk of chloroquine-resistant falciparum malaria.

Meningococcal meningitis

See *cerebrospinal meningitis*

Methadone

A medicine, belonging to the morphine family, used for pain relief, administered either orally or by subcutaneous or intramuscular injection.

Miltefosine

An anti-cancer medicine administered by mouth that is also being tested as an oral treatment for Leishmaniasis.

Morbidity

Levels of sickness and ill health.

Natural history of a disease

The description and classification of a disease, often with emphasis on the course of the disease without the influence of interventions.

Neglected diseases

Diseases which may be very common but because of market systems and lack of a population able to afford treatments, are not subject to wide-scale research and development.

Nevirapine (see also *Viramune*)

One of a class of medicines normally used in the treatment of progressive or advanced HIV infection, in combination with at least two other antiretroviral medicines. Recent studies have demonstrated the efficacy of the medicine in reducing perinatal transmission of HIV, where a single dose of the medicine is administered to the mother during labour and a single dose is given to the child within 72 hours of birth.

Non-communicable diseases (see also *communicable diseases*)

Diseases caused by factors other than living organisms, such as lifestyle, diet, genes or a combination of factors. Examples of non-communicable diseases include mental disorders, heart disease, and cancer.

Non-infectious diseases

See *non-communicable diseases*.

Onchocerciasis ('River Blindness')

Onchocerciasis is a parasitic disease transmitted by simulium flies, which breed in fast-flowing rivers and streams. The parasites migrate about the body, including to the eyes where they may cause blindness.

Pathogen

Any disease-causing agent, but particularly disease-producing micro-organisms.

Pathogenesis

The mode of production or development of a disease.

Perinatal transmission

Transmission of an infection-causing agent, such as HIV, from mother to child in the period either shortly before or after birth.

Pharmacogenetics

The study of how genetic differences influence the variability in patients' responses to medicines.

Placebo

A treatment known to be without effect, usually used as a control to be compared against a potentially effective substance or method which is being subjected to clinical trial.

Pneumonia

Inflammation of the lungs due to infection with micro-organisms.

Poliomyelitis ('polio')

A disorder caused by infection with the *poliovirus* that affects the whole body, including muscles and nerves. Severe cases may cause permanent paralysis or death. Transmission of the virus occurs by direct person-to-person contact, by contact with infected secretions from the nose or mouth, or by contact with infected faeces. An oral vaccine is available as a preventive measure. Any treatment is based on the presence and severity of symptoms, but may involve administration of antibiotics (e.g. for urinary tract infections) or analgesics (for pain relief), or moist heat to reduce muscle pain and spasm. In severe cases, life-saving measures, particularly to assist with breathing may be required. Interventions (e.g. physical therapy) to maximise recovery of muscle strength and function may also ultimately be needed.

Praziquantel

A medicine used in the treatment of blood fluke worm infections, which cause the disease schistosomiasis (also known as bilharziasis) (see *Schistosomiasis*).

Prophylactic

Preventive measure, including medication.

Prophylactic chemotherapy

Preventative medicine treatment for diseases such as tuberculosis and certain types of cancer (e.g. Non-Hodgkin's lymphoma).

Protease inhibitors

A class of medicines used in the treatment of HIV infection.

Quorate

A quorum is the minimum number of members that must be present to constitute a valid meeting, where decisions can be taken concerning submissions put forward for ethical review. A meeting is quorate when a quorum is present.

Randomised controlled trials

An experiment in which investigators randomly allocate eligible participants into control and intervention groups to receive one or more interventions that are being tested. The results are assessed by comparing outcomes of the two groups. (See also *Control*)

Rectal artesunate

An anti-malarial medicine administered as a suppository.

Rhinitis

Inflammation of the mucous membranes in the nose.

Rotavirus oral vaccines

Vaccines for immunisation against rotavirus, the commonest cause of severe diarrhoea among children worldwide.

Schistosomiasis

Also known as bilharziasis. Schistosomiasis is a disease caused by infestation with parasitic trematode worms. The disease is endemic in over 70 developing countries. The parasite enters the body through contact with infested surface water, mainly among people engaged in agriculture and fishing. Symptoms may initially include itchy skin and a rash, followed by fever, chills, cough, and muscle aches. It is common for people to present with no symptoms at the early phase of infection. In rare cases, seizures, paralysis, or spinal cord inflammation may occur. Repeat infection is possible which can result in damage to the liver, intestines, lungs, and urinary tract. Control of the disease may be directed at medicine treatment, control of the host (snails), improvements in personal hygiene or sanitation or a combination of all three.

Shaman

A shaman is someone who is believed to mediate between the spirit world and humanity, and is able to enter into a trance or similar state and then diagnose and prescribe or effect cures for disease. The term was originally coined by scholars who were studying societies in Siberia and central Asia, and was later extended to similar religious complexes found elsewhere in the world.

Sickle cell disease

A genetic disorder caused by an abnormality of the haemoglobin molecule, which carries oxygen in the blood. The disease is characterised by chronic haemolytic anaemia (a deficiency in the number of red blood cells caused by reduced cell survival time and the release of haemoglobin, which results in an insufficient supply of oxygen to tissues and organs), sickle-shaped deformity of the red blood cells, and complications relating to aggregations of sickle cells in blood vessels (e.g. infarction or death of tissue and bodily organs due to inadequate blood supply). The disease is only fully expressed in the homozygous state (i.e. where the gene has been inherited from both parents). The heterozygous state (when an abnormal gene has been inherited from one parent and a normal gene from the other) is thought to confer some protection against falciparum malaria in endemic areas.

Sleeping sickness

See *African trypanosomiasis*.

Stroke

A sudden impairment of brain function due to bleeding (haemorrhage) from or obstruction to one or more cerebral blood vessels.

Tetanus

Tetanus or 'lockjaw' is an acute, infectious disease caused by the anaerobic, spore-forming bacillus *Clostridium tetani*. The agent most often enters the body through contaminated puncture wounds (caused by, for example, rusty nails) or via other means such as burns and ulcers. The disease can be fatal as a result of respiratory difficulties or exhaustion.

Tiered pricing

Differential pricing of medicines based on consideration of a country's economic status.

Titre

The quantity of a substance required to produce a reaction with, or correspond to, a given quantity of another substance.

Trachoma

Trachoma is caused by the bacteria *Chlamydia trachomatis*, which is highly contagious. Repeated infections cause eyelashes to turn inwards, scarring the eye and leading to blindness in adult life.

Tuberculosis

A serious infectious disease caused by a species of *Mycobacterium*. The disease can involve almost any organ or tissue of the body, but the lungs are most commonly affected. Symptoms include a persistent

cough, fever, weight loss, constant tiredness, and loss of appetite. The disease is highly contagious and is spread through the air.

Vector

An animal carrier of the agent of a communicable disease.

Viramune

The brand name for nevirapine (see *Nevirapine*).

Yellow fever

An acute viral infection caused by a group B arbovirus and transmitted by mosquitoes of the *Aedes* and *Haemagogus* type. The disease varies in severity from a mild influenza-like episode to a dangerous and sometimes fatal illness marked by jaundice due to liver necrosis, haemorrhaging (bleeding), and renal failure.

Yunani

A branch of traditional medicine, common to Muslim areas on the Indo-Pakistan subcontinent. This is the medicine of the ancient Greeks, translated into Arabic and Persian and then slowly modified by its practitioners, the Hakim. The system is based around the four humors: yellow bile, black bile, phlegm, and blood, which combine with four primary qualities of heat, cold, moisture, and dryness. Illness is thought to result from the disequilibrium of the humors and qualities.

Zentel

Brand name for the medicine Albendazole (see *Albendazole*).

Zidovudine

An antiviral medicine now used mainly in developed countries in the triple medicine combination for the treatment of HIV/AIDS.

Zithromax

Brand name for the medicine Azithromycin (see *Azithromycin*).

Glossary of Acronyms

AIDS	Acquired immune deficiency syndrome
AMA	American Medical Association
AMRC	Association of Medical Research Charities (UK)
AMVTN	The African Malaria Vaccine Testing Network
AZT	Azidothymidine (more recently called zidovudine)

CDC	Centers for Disease Control and Prevention (US)
CHRD	Commission on Health Research for Development (Switzerland)
CIOMS	Council for International Organizations of Medical Sciences
COHRED	Commission on Health Research for Development
CONEP	Central Committee of Ethics in Clinical Research (Brazil)
CPMP	Committee for Proprietary Medicinal Products (Europe)
CSM	Cerebro-spinal meningitis
DALYs	Disability adjusted life years
DfID	Department for International Development (UK)
DHHS	Department of Health and Human Services (US)
DSMC	Data and safety monitoring committee
EC	European Commission
EFGCP	European Forum for Good Clinical Practice
ENHR	Essential national health research
FDA	Food and Medicine Administration (US)
FECCIS	Forum for Ethics Committees in the Confederation of Independent States
FERCAP	Forum for Ethical Review Committees in the Asian and Western Pacific Region
FERCIT	Forum of Ethical Review Committees in Thailand
FLACEIS	Foro Latino Americano de Comités de Ética en Investigacion en Salud
GAVI	Global Alliance for Vaccines and Immunization
GNP	Gross national product
GOBI-FFF	Growth monitoring, oral rehydration, breastfeeding, immunization, food supplementation, family planning, and female education
GPPP	Global public private partnership
GSK	GlaxoSmithKline
HAVEG	HIV/AIDS Vaccine Ethics Group (University of Natal, South Africa)
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HIV-NAT	The HIV Netherlands Australia Thailand Research Collaboration
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation
ICDDR-B	International Centre for Diarrhoeal Diseases Research, Bangladesh
ICMR	Indian Council of Medical Research
IRB	Institutional review board
MHC	Maori Health Committee (of the Health Research Council of New Zealand)
MMV	Medicines for Malaria Venture
MRC	Medical Research Council (UK)
MRI	Magnetic resonance imaging
MVI	Malaria Vaccine Initiative
NBAC	National Bioethics Advisory Commission (US)
NGO	Non-governmental organisation
NHMRC	National Health and Medical Research Council (Australia)
NIH	National Institutes of Health (US)
PABIN	Pan African Bioethics Initiative
PAHO	Pan American Health Organization
PhRMA	Pharmaceutical and Research Manufacturers of America
PRISM	Unit for Policy Research in Science and Medicine (UK)
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
STD	Sexually transmitted disease
TB	Tuberculosis

TDR	UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WMA	World Medical Association
WTO	World Trade Organization

Index

Aboriginal and Torres Strait Islanders, research guidance 63, 76, 150
adverse effects
  giving information on 75
  post-trial responsibilities 116–18, 153–4
  see also risks, research
Afghanistan, infant mortality 16, 17
Africa
  consent 44–5
  ethical review 109
  health indicators 15, 16, 17, 19
  schistosomiasis 92
  traditional medicine 40
  see also specific countries
African Malaria Vaccine Testing Network (AMVTN) 109
after the trial *see* completion, study
AIDS *see* HIV infection/AIDS
albendazole 30, 31
alternative medical systems 39, 178
altruistic beliefs 45–6
American Medical Association (AMA) 60
Angell, Marcia 8, 89
annual reports, research progress 107
Anopheles stephensi 25
antimalarial drugs 33, 121–2
antiretroviral drugs
  costs 33–4, 122
  pregnant women 8, 93, 117, 122, 124
Argentina 104
artemisinins 33
Asia
  disability-adjusted life expectancy 16
  ethical review 109
audio tapes 74, 82
Australia, national guidance 63, 76, 150, 151
autonomy, individual 43, 57
Ayurvedic system 39
azithromycin 26, 31

basic research 25, 163
bed-nets, insecticide-impregnated 31, 118, 119, 123
behavioural research 25, 163
belief systems, local 40–2, 74–5
Belmont Report (1979) 64, 150, 159
beneficence 57
benefits (of research) 125, 177
  duty to provide 53, 90–1
  indirect 29, 31, 131
  to participants 78, 79, 91, 115, 131
Bill and Melinda Gates Foundation 27, 29
blood samples 41, 71
Brazil
  consent 76
  ethical review 104
  national guidance 151, 152, 153, 156–7
Burkina Faso 40
Burkitt's lymphoma 29, 31

Canada, national guidance 151
cancer
  diagnosis 73
  liver 93
  screening 25, 89
capacity (to give consent) 76–7
Caribbean 19, 109
Centers for Disease Control (CDC) 27
cerebro-spinal meningitis 8
cervical cancer screening 25
charities 27, 29
child mortality rates 16–17, 18
  interventions reducing 31, 122–3
children
  immunisation 17
  participation in research 44, 71, 76–7
Chile, motivation of participants 45–6
China
  community consultation 44
  national guidance 151
  traditional medicine 39
chloroquine 33
chronic disease 103
CIOMS/WHO guidelines 58, 59, 61–2, 157
  on consent 72, 78, 79, 80
  enforcement 65
  on ethical review 101, 154
  on post-trial responsibilities 114, 115, 116
  on standards of care 88
clinical research 25, 163
clinical trials 28–9, 163
  for benefit of developed countries 125
  control groups *see* control groups
  implementing results 113, 120–1
  international guidance 61, 62
  national guidance 64
  standards of care 61, 62, 89–92
  supply of drugs for 34
co-artemether 33
collaborative research projects 126
Colombia, consent 45
colonialism, legacy of 46
Commission on Health Research for Development 21–2, 26, 30, 125–6
communicable diseases 17, 19
  need for new interventions 32
communication infrastructure 21
community
  assent/involvement 43–4, 71, 76–7, 135
  consultation 43, 44, 74, 75–6, 133
  implementing research results 113, 116, 119, 121–2, 142–3
  respect for 43
community leaders
  assent/involvement 76–7, 135
  trust in/respect for 43
compensation
  for adverse effects 116–17, 153–4
  see also fees; payments
competence (to give consent) 71
complementary therapies 39
completion, study 9–10, 113–26, 141–3
  consultation views 180
  ethical review of arrangements 103
  guidance 61, 62, 114–15, 120, 121–2, 156
  recommendations 116, 120, 121, 125, 126, 141, 142–3
condoms 31
confidentiality 7, 73
conflicts of interest 105, 180
consent 6–7, 71–83, 135–7
  community involvement 76–7, 135
  confidentiality issues 7, 73
  cultural issues 43–6, 52, 72–3, 80, 177–8
  essential elements 65
  ethical review of procedures 81–2, 83, 103
  forms 7, 80–3, 136–7
  genuineness 71–3, 77, 135
  information for *see* information
  recommendations 77, 80, 83, 136, 137
  recording 80–3, 136–7
  refusal 77–8, 136
  verbal 82, 83, 137
  voluntariness 71, 75–80, 135–6
contraceptives 31
control groups
  placebo therapy 8, 61, 62
  post-trial care 118, 119–20, 142
  standards of care 7, 61, 89–97, 138–9
cost-benefit analysis 122
costs
  drug development 32–3
  fall over time 9, 34, 123–4
  interventions 9, 31, 33–4, 123–4, 180–1
  research ethics committees 106–7, 140
Cote d'Ivoire 93
Council on Health Research for Development (COHRED) 26
Council for International Organisations of Medical Sciences guidelines *see* CIOMS/WHO guidelines

cultural assistants 42
cultural context 39–46, 133
  consent 43–6, 52, 72–3, 80, 177–8
cultural differences, sensitivity to 51–2, 134
  conflicts 77, 135
  in practice 53, 73, 135
Czech Republic 104

Data and Safety Monitoring Committee (DSMC) 116
death, concepts of 40–2
decision making, about research 43–4, 71, 75–7
Declaration of Helsinki *see* Helsinki Declaration
Denmark, national guidance 63
Department for International Development (DFID) (UK) 25, 27, 28
designs, research 93, 138, 163
diagnosis, information about 73, 135
diarrhoeal diseases 34
disability-adjusted life expectancy 16
disability-adjusted life years (DALYs) 17, 19
disease, concepts 40–2
doctors
  ethical guidance 65
  numbers 20, 21
  patient relationships 42–3, 73
  trust in/respect for 41, 78
drugs *see* medicines

economic context 15–35, 132
education 21
  see also training
elders, community *see* community leaders
elephantiasis 31
empire, legacy of 46
epidemiological research 25, 62, 163
equality 90, 137–8
equipment, research 126, 143
essential national health research (ENHR) strategies 26–7
Ethical Considerations in HIV Preventive Vaccine Research (UNAIDS) 58, 59, 62, 157
  on ethical review 101
  on post-trial responsibilities 114
  on standards of care 88, 96, 139
ethical framework 49–53
ethical principles 6, 49–53, 131, 133–4
  alternative terminology 57
  key 178
  translation into practice 53
ethical review 9, 101–9, 140–1
  consent procedures 81–2, 83, 103
  developing capacity for 108–9, 132
  guidance 101, 105, 154–6
  issues to be considered 167–9
  levels of assessment 102, 140
  post-trial aspects 142–3
  recommendations 102, 106–7, 108–9, 140–1
  requirements for effective 103–6
  in sponsor and host countries 107–8, 140–1
  versus scientific review 102
  see also ethics committees, research
ethics committees, research 9, 53, 101–9, 140–1
  ad hoc decisions 104–5
  conflicts of interest 105, 180
  consultation views 180
  countries lacking 104, 105
  disagreement between 107, 141
  financial support 106–7, 140
  frequency of meetings 106
  independence 106–7, 140
  membership 105
  requirements for effective 103–6, 140
  training of members 105, 108–9, 141
Europe
  ethical review 104, 109
  research funding 27, 28
  research guidance 58, 64, 157
evidence base 22
expenditure, research
  by external sponsors 22–3, 24
  premature mortality and 21–2
expertise, developing local
  in healthcare 116, 141
  for research 22, 125–6, 131–2, 143
  see also training
exploitation, avoidance of 52–3, 57, 131, 134
  inducements and 79
  post-trial access to interventions and 113, 118
  standards of care and 90, 137
externally sponsored research
  ethical review 102, 107–8, 140–1
  guidance 57, 64
  recommendations 131
  relevance to local priorities 27, 28–30, 131
  scope 22–4

fact-finding meetings 173–4
faeces, samples of 41
fairness *see* justice
family
  decisions about research 43–4, 71
  respect for 43
  senior members, assent by 76–7, 137
Fansidar 33
feasibility studies 25
fees
  to research ethics committees 106, 140
  see also payments
filariasis, lymphatic 31
financial support *see* funding
Finland, national guidance 151
Fogarty International Center 108
Food and Drug Administration (FDA) 22–3
fora, regional, for developing capacity for ethical review 108, 109
France, national guidance 150
funding
  agencies, research *see* sponsors, research
  research ethics committees 106–7, 140

The Gambia
  consent 82–3
  Haemophilus influenzae type b vaccine 34, 119, 124
  hepatitis B vaccination 9, 124
  HIV vaccine 28
  insecticide-treated bed-nets 123
genetic research 34–5, 75
Geneva Declaration 147
Ghana, traditional medicine 40
GlaxoSmithKline (GSK) 29, 30
Global Alliance for Vaccines and Immunization (GAVI) 27, 30
global public-private partnerships (GPPPs) 23, 27, 32
GOBI-FFF 122–3
goitre 123
good clinical practice guidelines 62
governmental bodies, funding research 27, 28
governments
  decisions on levels of care 138
  funding research ethics committees 106
  implementing trial results 122, 123–5, 142–3, 180–1
gross national product (GNP)
  per capita, life expectancy and 17–20
  proportion spent on health 20–1
guidance 57–66, 134–5, 147–59
  available on internet 157–9
  completion of study 61, 62, 114–15, 120, 121–2, 156
  consent 71, 78
  consultation views 179–80
  contradictory 65, 66
  enforcement 64–5, 179
  ethical review 101, 105, 154–6
  historical context 57–8
  implementation 59
  information provision 60–1, 72
  international 58, 59–62
  national *see* national guidance
  recommendations 66, 134–5
  standards of care 57, 61, 87–8, 96, 152–4

guidance (*continued*)
training in interpreting/applying 65–6, 134–5
see also specific guidelines
Guidance on Good Clinical Practice (ICH) 62, 88, 101, 154, 157
Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products (WHO) 62, 88, 101, 114, 157
Guinea Bissau 104, 117–18

Haemophilus influenzae type b (Hib) vaccine 34, 119, 124
halofantrine 33
harm
prevention of avoidable 91–2, 117
see also risks, research
healers, traditional *see* traditional healers
health
determinants 5
inequalities 15–17, 131, 132
healthcare
continuation of improvements 115–16
development of local expertise 116, 141
implementing changes 122–3
as inducement to participate 78, 79, 136
research needs 5–6
resources, variations between countries 17–21
standards *see* standards of care
see also interventions; treatment
healthcare workers
information provision 74, 78
trust in/respect for 42
health expenditure
per capita 20
as proportion of GNP 20–1
health systems
research 26, 163
standards of care available 94
Helsinki Declaration 58, 59–61, 147–50, 157
on consent 72, 78
enforcement 65
on ethical review 101
on post-trial responsibilities 114, 115, 120
revisions 60
on standards of care 61, 87, 88
hepatitis B vaccine 9, 34, 124
hepatitis E 30
HIV
counselling and testing 9, 25
drugs *see* antiretroviral drugs
research sponsors 27, 28, 30
vaccines 25, 27, 28, 96, 139
HIV infection/AIDS 5, 17
confidentiality issues 7, 73
donation of condoms 31
low-cost treatment 8, 125
perinatal transmission trials (1997) 6, 7, 8, 57, 93–4
prevention of perinatal transmission 93, 117, 122, 124
standards of care 95
STDs and 95, 97
TB prophylaxis 95
traditional healthcare 40
human immunodeficiency virus *see* HIV

ICH *see* International Conference on Harmonisation
illiterate populations, recording consent 17, 81, 82, 136–7
illness
concepts 40–2
in preventive studies 96
unrelated, standard of care 97, 139
immune cells 75
immunisation, childhood 17
implementation, research results 9–10, 113, 119–25, 142–3
India
ethical review 104
infant mortality rates 16–17
national guidance 117, 151, 152, 155, 156
inducements 71, 78–80, 103, 136, 178–9
see also payments
infant mortality rates 16–17
infectious diseases *see* communicable diseases
information 43, 71–5, 133, 135
on complex and novel concepts 74–5
ethical review of procedures 103
guidance 60–1, 72
on post-trial interventions 120
on research results 123
sheets 81, 82, 83, 136
understandable 74
infrastructure development 21
injections 41
insecticide-impregnated bed-nets 31, 118, 119, 123
international agencies 27–8
post-trial responsibilities 123–5, 142–3
International AIDS Vaccine Initiative (IAVI) 27, 32
International Code of Medical Ethics 147
International Conference on Harmonisation (ICH) 58, 59, 65, 157
on ethical review 101, 154
on standards of care 88
International Ethical Guidelines for Biomedical Research Involving Human Subjects *see* CIOMS/WHO guidelines
International Guidelines for Ethical Review of Epidemiological Studies *see* CIOMS/WHO guidelines
International Trachoma Initiative (ITI) 26
interpreters 42, 78
interventions
adverse effects *see* adverse effects
affordability 9, 31, 33–4, 113, 123–4, 180–1
developing new 30–4
donated/subsidised 31, 33–4
evidence base 22
post-trial availability 103, 113–16, 118–25, 141, 142–3
see also treatment
intervention studies 163
investigators *see* researchers
iodination of salt 123
isolated areas, standards of care 96
ivermectin 31, 124
Ivory Coast 7

Jamaica, ENHR strategy 26
Japan 16, 17
justice 57, 90, 131, 137

The Lancet 8, 9
lancets 91
language 63, 72
Laos 104
Latin America
consent 45
ethical review 104, 109
health indicators 16, 19
US-sponsored research 23, 24
lay members, research ethics committees 105
leaders, community *see* community leaders
legal liability 81
leprosy 7
life expectancy
disability-adjusted 16
GNP per capita and 17–20
trends 17, 21
variations between countries 15–17
liver cancer 93
lung cancer screening 89

malaria 25
affordable interventions 31
expenditure on research 23
medications 33, 121–2
post-trial care/surveillance 118, 119
public-private partnerships 23, 27
research sponsors 27, 28, 30
traditional healthcare 40
vaccines 109, 117
Malaria Vaccine Initiative (MVI) 27, 30
Malarone 27, 31, 33
Malawi, blood samples 41

Maori communities 63, 76
measles vaccines 117–18
Medical Research Council (MRC) (UK)
  guidance 71, 151, 152, 156, 158
  research funding 25, 27, 28, 117, 123
Medical Research Council of South Africa 126, 151, 158
medicines
  development of new 32–3, 34–5
  donated/subsidised 31, 33–4, 124
  generic versions 33–4
  see also vaccines; *specific drugs*
Medicines for Malaria Venture (MMV) 23, 27
meetings
  fact-finding 173–4
  public 43, 74, 123
mefloquine 33, 121
men, decision making by 43–4, 45
meningitis
  cerebro-spinal 8
  meningococcal 96
Michigan State University 25
misfortune, concepts of 40–2
molecular medicine 34–5
monitoring
  post-trial 116–18, 142–3
  by research ethics committees 107, 142
moral relativism 51–2, 134
mortality, research expenditure and 21–2
mosquitoes, malaria 25
mothers-in-law 44
motivation, research participants 45–6, 78, 136
multi-disciplinary research 66
Myanmar 104

National Bioethics Advisory Committee (NBAC) (US) 46, 64, 158
  on consent 82
  on post-trial access to interventions 103, 115, 120, 121, 156
  on standards of care 152, 154
national guidance 62–4, 150–1
  available on internet 158–9
  development 65, 66, 135
  on specific topics 152–7
National Institutes of Health (NIH) (US) 63, 108, 123
national priorities for research, setting 24–7, 28, 132–3
national standards of care 94–5, 138–9
natural history of disease 25
neglected diseases 32–3
Nepal, national guidance 151
Netherlands, national guidance 151
nevirapine 124
New England Journal of Medicine 8, 89
New Zealand, national guidance 63, 76, 151
Nigeria 96, 122–3
non-therapeutic research 61, 71
Nuremberg Code 57–8
nurses, numbers of 20, 21
nutrition 21

onchocerciasis 31, 124
operational research 163
oral rehydration solution 34

Pakistan 41
Pan African Bioethics Initiative (PABIN) 109
participants, research
  belief systems 41–2
  benefits to 78, 79, 91, 115, 131
  compensation for injury 116–17, 153–4
  consent *see* consent
  continuing care 10, 61, 103, 113–21, 142–3
  decision making by 43–6
  illness developing in 8, 96, 139
  inducements 71, 78–80, 103, 136, 178–9
  information for 43, 60–1, 71–5
  motivations 45–6, 78, 136
  post-trial surveillance 116–18, 142–3
  therapeutic misconception 46
  see also control groups
payments
  as inducements to participate 78, 146
  to members of research ethics committees 105
  see also fees
pharmaceutical companies 27
  drug development 32–3, 34–5
  ethical guidance 65
  fees to research ethics committees 106
  free/subsidised medicines 31, 33–4, 124
  overseas research by US 23, 24
  post-trial responsibilities 121, 123, 124, 142, 180–1
  research priorities 28–30
  scientific review of proposed research 102
Pharmaceutical Research and Manufacturers of America (PhRMA) 22, 23, 24
pharmacogenetics 33–4
Philippines 79
physicians *see* doctors
placebo 71, 163
  controlled trials 8, 61, 62
  defined 7
  explaining 75
policy-makers 122
post-trial issues *see* completion, study
poverty 131
power imbalances
  developed/developing countries 29–30, 52, 107, 131
  doctors and patients 42
  see also exploitation, avoidance of
praziquantel 34, 92
pregnancy
  antiretroviral therapy 8, 93, 117, 122, 124
  place of confinement 43
preventive studies
  care of participants 8, 96
  long-term surveillance after 117–18
priorities, research 24–30, 132–3, 177
  ethical review 102, 140
  external sponsors 27–8, 131
  pharmaceutical companies 28–30
  recommendations 30, 132–3
  setting national 24–7, 30, 132–3
privacy 73
private healthcare 94
proportionality, inducements 80
proxy, consent by 76–7
publication, research results 57
Public Citizen 32, 60
public meetings 43, 74, 123
public-private partnerships
  defined 27
  global (GPPPs) 23, 27, 32

quinine 33

radio 74
randomisation 75
refusal to participate 77–8, 136
regional fora for developing capacity for ethical review 108, 109
relativism, moral 51–2, 134
religious representatives, research ethics committees 105
remuneration *see* payments
research
  needs 5–6
  types 24, 25–6, 163
researchers
  implementation of guidance 59
  post-trial responsibilities 113, 116, 117–18, 122–3, 125, 141–3
  standards of care provided 90–1
resources
  to conduct research 22
  healthcare, variations between countries 17–21
  inequitable distribution 15, 49
respect for persons 51, 57, 133–4
  conflicts 77, 90, 135

respect for persons (*continued*)
consent and 71
standards of care and 137–8
results, research
implementation 9–10, 113, 119–25, 142–3
reporting and publication 57, 123
risks, research
giving information on 75
level of inducements and 79, 80
limiting legal liability 81
see also adverse effects
river blindness 31, 124
Russia 104, 109

safari research 126
salt, iodination 123
sanitation 21
schistosomiasis 34, 92
scientific principles 57
scientific validity, review 102, 140, 167
screening, cancer 25, 89
Senegal 117–18
sexual behaviour, high-risk 25
sexually transmitted diseases (STDs) 95, 97
shamans 40, 42, 43
side-effects *see* adverse effects
sleeping sickness 25
social context 39–46, 72–3, 133
social research 25, 163
socio-economic context 15–35, 132
South Africa
national guidance 115, 126, 151, 152, 156
women 45, 77–8
South-East Asia 91
Special Programme of Research, Development and Research Training in Human Reproduction 108
Special Programme for Research and Training in Tropical Disease (TDR) 27–8, 108, 121, 154
spirits, affliction by 40–1
sponsors, research 6, 27–8
funding research ethics committees 106–7
post-trial responsibilities 113, 116, 117–28, 123–5, 141–3, 180–1
priorities 27–30, 131
scientific review by 102
standards of care provided 90–1
see also externally sponsored research; pharmaceutical companies
standards of care 7–8, 87–97, 137–9
appropriate 89–92
consultation views 179
ethical review 103
guidance 57, 61, 87–8, 96, 152–4
importance of context 92–4
national 94–5, 138–9
non-universal 89, 94–7, 137
in preventive studies 96
recommendations 94–5, 96, 97, 139
universal 89, 92–4, 137
unrelated illnesses 97, 139
Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) 108
subjects, research *see* participants, research
suffering, alleviation of 50, 51, 57, 90–1, 133–4
surveillance *see* monitoring

Tanzania 25
Task Force on Health Research for Development 26, 30
10/90 disequilibrium 21–2
tetanus, neonatal 122
Thailand
ethical review 109
HIV 7, 25, 93–4
motivation of participants 45
national guidance 151
research priorities 27
therapeutic misconception 46
therapeutic research 61, 71
trachoma 26, 31
traditional healers 40, 133, 178
client relationships 42–3
traditional medical systems 39
combined with modern healthcare 40
training
in equipment maintenance 126, 143
in information provision 74
in interpreting/applying guidance 65–6, 134–5
members of research ethics committees 105, 108–9, 141
in research expertise 22, 125–6, 131–2, 143
see also expertise, developing local
treatment
best current method 88–9, 93–4
conditions arising during study 91
as inducement to participate 79
research incorporating 61, 71
standards *see* standards of care
see also healthcare; interventions
Trypanosoma brucei rhodesiense 25
tuberculosis (TB)
prophylaxis 95
research funding 27, 28, 30
Tufts Center for the Study of Drug Development 32

Uganda
consent 44
ENHR strategy 26
HIV 25, 124
national guidance 63, 115, 120, 151, 152, 155, 156
sleeping sickness 25
Ukraine 104
umbilical cord care 41
UNAIDS *see* Ethical Considerations in HIV Preventive Vaccine Research
UNESCO 58, 71
UNICEF 122–3
United Kingdom (UK)
national guidance 150, 151, 152, 153, 155
research funding 27, 28
United Nations 58
United Nations Population Fund (UNFPA) 25
United States (US)
consent 71
healthcare expenditure 20
infant mortality rates 17
national guidance 63–4, 150, 151, 152, 156
research overseas 22–3, 27
unsafe practices, avoiding 91–2
urine samples 41

vaccines 5
care of study participants 8, 96, 119–20
cerebro-spinal meningitis 8
costs 34
development of new 32
donated/subsidised 31, 124
VaxGen 25
Venezuela, leprosy study 7
video tapes 74
Vietnam 65
violence, domestic 82
vitamin A supplements 31
vulnerable populations
avoidance of exploitation *see* exploitation, avoidance of
ethical issues 169
levels of inducement 80
represented on research ethics committees 105

water 21
Wellcome Trust, The 23, 27, 29
withdrawal, study 78
witnessing verbal consent 82, 83, 137
women
decision making by 44–6, 71, 77–8
on research ethics committees 105

World Health Organization (WHO) 179
disability-adjusted life expectancy 16
research guidelines 58, 62
research priorities 24–6
see also CIOMS/WHO guidelines; Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products
World Medical Association (WMA) 58
Helsinki Declaration *see* Helsinki Declaration
World Trade Organisation (WTO) 33

Yunani system 39

Zentel 30
zidovudine, for pregnant women 8
Zimbabwe, cervical cancer screening 25
Zithromax (azithromycin) 26, 31

Genetic screening: ethical issues
Reprinted October 1997

Human tissue: ethical and legal issues
Published April 1995

Animal-to-human transplants: the ethics of xenotransplantation
Published March 1996

Mental disorders and genetics: the ethical context
Published September 1998

Genetically modified crops: the ethical and social issues
Published May 1999

The ethics of clinical research in developing countries: a discussion paper
Published October 1999

Stem cell therapy: the ethical issues – a discussion paper
Published April 2000

NUFFIELD COUNCIL ON BIOETHICS

Published by
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3JS

Telephone: 020 7681 9619
Fax: 020 7637 1712
Internet: www.nuffieldbioethics.org